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Chapter

Childhood Idiopathic Nephrotic Syndrome as a Podocytopathy

Samuel N. Uwaezuoke

Abstract

Idiopathic nephrotic syndrome is the commonest manifestation of glomerular disease in children. The syndrome is characterized by massive proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia. Although genetic or congenital forms are now well recognized, nephrotic syndrome is largely acquired. The latter form can be idiopathic or primary (the causes are unknown) and secondary (the causes are known renal or non-renal diseases). Idiopathic nephrotic syndrome consists of the following glomerulonephritides: minimal change nephropathy (MCN), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis (MesPGN), and membranous nephritis (MN). The etiopathogenesis of nephrotic syndrome has evolved through several hypotheses ranging from immune dysregulation theory and increased glomerular permeability theory to the current concept of podocytopathy. Podocyte injury is now thought to be the basic pathology in the syndrome. The book chapter aims to highlight the mechanisms underlying the pathogenesis of nephrotic syndrome as a podocytopathy.

Keywords: idiopathic nephrotic syndrome, glomerular disease, glomerulonephritides, podocyte injury

1. Introduction

Nephrotic syndrome is the commonest manifestation of glomerular disease which is characterized by massive proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia [1]. In children, primary or idiopathic nephrotic syndrome (INS) may be caused by any of these glomerulonephritides: minimal change nephropathy (MCN), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis (MesPGN), and membranous nephropathy (MN). MCN appears to be the most common histopathologic type, followed by FSGS and MPGN in that order [2–4]. However, recent reports from different parts of the world suggest a change in the pattern of the predominant histopathologic types in childhood INS. For instance, there has been a rise in the prevalence rates of FSGS documented among children in the West African subregion [5–7]. This trend also applies to MPGN [8], a histological subtype hitherto thought to be more common in adult patients.

In the pathogenesis of INS, there is now a paradigm shift from the concept of an immune-dysregulated disease of the glomerular basement membrane to that of a podocytopathy [9, 10]. In fact, it is now assumed that podocyte abnormalities account

for all forms of nephrotic syndrome. Basically, the podocyte is involved in maintaining the structural integrity of the glomerular filtration barrier. Thus, podocyte injury and loss result in significant proteinuria as well as progressive glomerulosclerosis [11]. Podocytopathy can occur in immunologic and non-immunologic diseases of the kidney. Acquired podocytopathies such as MCN and FSGS are considered to have immunologic basis [12]. Interestingly, immunosuppressive therapy has been noted to directly affect the podocyte through the regulation of interleukin-4 (IL-4) and interleukin-13 (IL-13) and several signaling pathways involved with the stabilization of the actin cytoskeleton and the distribution of the slit diaphragm components [11]. This book chapter aims to discuss the mechanisms underpinning the pathogenesis of childhood INS as a podocytopathy.

2. The molecular structure and function of the podocyte

The glomerular filtration barrier is essentially a trilaminate structure which consists of the podocyte on the outer surface, the glomerular basement membrane (GBM) in the middle, and the fenestrated endothelium on the inner surface (**Figure 1**). The podocyte (also known as the visceral glomerular epithelial cell) constitutes the last barrier to protein loss, given its unique structure and location as a terminally differentiated cell which lines the outer surface of the GBM. Each podocyte comprises the foot processes which are separated by a filtration slit (or the slit diaphragm). The foot process comprises components such as actin, myosin-II, α-actinin-4, talin, and vinculin which all constitute a contractile structure [13]. The filament bundles which make up actin are disposed together as arches between contiguous podocyte foot processes [14] and are connected to the GBM at specific points through an adhesion molecule (α-3β-1 integrin complex) [15, 16]. Similarly, the linkage of the podocyte foot processes to the GBM is made possible through both α-3β-1 integrin and dystroglycans [17]. Adjacent foot processes are linked by the slit diaphragm, which forms the main size-selective filter barrier in the glomerular architecture [18, 19]. The filtration slit is composed of multiple protein molecules such as nephrin, P-cadherin, CD2AP, ZO-1, FAT, podocin, and possibly

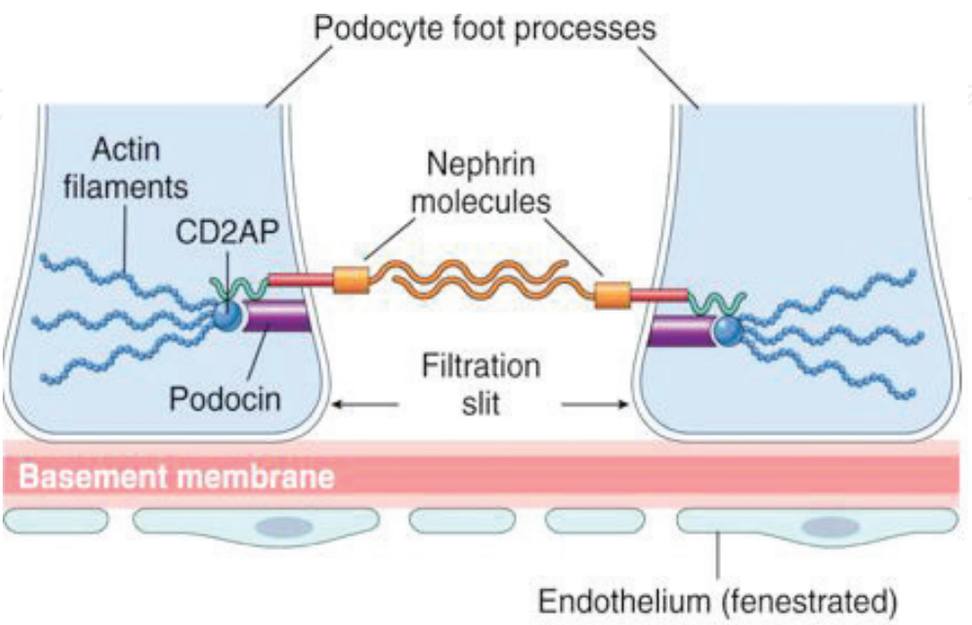

Figure 1.
Schematic representation of the molecular structure of the glomerular filtration barrier (Courtesy: Flickr photos).

Neph1 [20–22]. In addition, synaptopodin is closely related to the actin filaments located within the podocyte foot processes [23] and interacts with the tight junction protein, MAGI-1, in the same way as α-actinin-4 MAGI-1 being expressed in podocytes as well [24]. The functional integrity of the podocytes depends on the actin cytoskeleton. This is critical in preserving the intact glomerular filtration barrier, as a healthy podocyte is essential for the maintenance of this barrier.

2.1 The molecular mechanisms in podocytopathy

Among the fundamental biologic events in INS, a molecular disruption of the filtration slit or GBM results in proteinuria, while rearrangement of podocyte cytoskeleton accounts for foot process effacement. In fact, the basic role played by the podocyte actin cytoskeleton (the skeletal structure of the foot processes) in the pathogenesis of INS is predicated on the disruption of actin-related proteins with the GBM, resulting in effacement of the podocyte foot processes [25]. Still at the molecular level, focal adhesion kinase (FAK) plays an essential role in this foot process effacement, usually observed in podocytopathies [26]. Furthermore, alterations in podocyte proteins such as nephrin and Neph1 (nephrin homologue), CD2-associated protein (CD2AP), and podocin all contribute to the pathogenesis of INS as podocytopathies [27–29]. Nephrin represents an essential constituent of the slit diaphragm and also serves as an efficient mobilizer of other proteins such as podocin and CD2AP (**Figure 1**) [30]. It has been proposed that a vital interaction exists between the actin cytoskeleton and the molecules that make up the filtration slit such as podocin, nephrin, and CD2AP [31, 32]. Thus, nephrotic-range proteinuria occurs as a result of structural disruptions in the podocytes which present as foot process effacement, as well as changes in the actin cytoskeleton and molecular alteration of the filtration slit [33]. Again, the component molecules of the actin cytoskeleton include actin, α-actinin, and synaptopodin [34, 35]. Interestingly, the upregulation of α-actinin results in the reorganization of the cytoskeleton in some nephrotic syndromes [36], while the expression of synaptopodin is generally preserved in MCN, but diminished in FSGS [37]. Podocalyxin is a molecule presumed to mediate the stability of the foot processes [38] and has also been found to be raised in nephrotic syndromes [39]. Finally, the fundamental role of adhesion molecules such as integrins and focal adhesion proteins has been shown in genetically based animal experiments which end up in nephrotic syndrome [40, 41]. Specifically, α3β1 (the main integrin heterodimer in the podocyte), when destroyed in the podocytes of experimental mice, gave rise to nephrotic-range proteinuria and foot process effacement. In addition, αvβ3 integrin (also expressed in podocytes) can be activated by uroplasminogen type I activator receptor (uPAR) (in podocytes) [42] or its soluble form, suPAR (from the circulation) [43]. Its activation notably leads to foot process effacement through the rearrangement of the podocyte actin cytoskeleton: a characteristic event in podocytopathy [44].

3. Treatment targets in the podocytopathy model

Interventions targeting molecular pathways which regulate the actin cytoskeleton can potentially play an important role in the treatment of proteinuric kidney diseases, such as nephrotic syndrome. There are three major molecular frameworks which modulate the actin cytoskeleton and prevent podocyte detachment from GBM, namely, Rho-GTPases, cell-matrix adhesion proteins, and endocytic proteins. For instance, the podocyte-expressed RhoA, Rac1, and Cdc42 regulate signal transduction pathways which affect many aspects of cell behavior, including alterations

in the actin cytoskeleton [45, 46]. The regulatory ability of these protein molecules on the actin cytoskeleton points to their fundamental role in the pathogenesis of nephrotic syndrome and as possible treatment targets [25]. For instance, the inhibition of RhoA and Rac1 could potentially reduce proteinuria and optimize renal function and ameliorate glomerulopathy [47–50], given that elevated RhoA activity has been noted to induce foot process effacement and subsequent proteinuria [51].

Furthermore, blocking αvβ3 integrin with an anti-β3 antibody or cilengitide (the small molecule inhibitor) was noted to have ameliorated uPAR-induced proteinuria, underscoring the importance of this integrin as another potential therapeutic target [42, 43]. Also, targeted pharmacologic inhibition of integrin α2β1 in murine models also reduced proteinuria [52], while inhibition of major focal adhesion proteins, such as FAK and Crk1/Crk2, reduced both podocyte foot process effacement and proteinuria [26, 53]. In addition, one important therapeutic target in proteinuria is the regulating activation of integrin β1 via abatacept (CTLA-4-Ig) or integrin αv inhibitor, cilengitide, or integrin α2β1 [42, 43, 52, 54].

The link between transient receptor potential cation channels (TRPCs) and the actin cytoskeleton has also been well reported [25]. TRPCs are nonselective cationic channels with affinity for calcium ions, which contribute significantly in the pathogenesis of renal and cardiovascular diseases [55]. In podocytes, many

Potential pharmacologic agents	Treatment targets in podocytopathy	Indications	Efficacy	Side effects
Cyclosporine A† (a major calcineurin inhibitor. Another example is FK 506)	Downregulation of synaptopodin	Clinical use in SRNS and in renal transplantation	Induces remission in SRNS	Major side effects in humans: tremors, hypertension, nephrotoxicity, hirsutism, and gum hypertrophy
Inhibitors of small Rho-GTPases‡	Small Rho-GTPases (Rho A, Rac 1)	Still under trial (nephrotic syndrome)	–	–
Cilengitide/anti-β3 antibody*	Blockage of αvβ3 integrin	Still under trial (nephrotic syndrome) Clinical use in glioblastoma	–	–
Abatacept	Modulating activation of integrin β1	Still under trial/ clinical use in FSGS	–	–
Inhibitors of TRPC 5**	TRPC 5	Still under trial	–	–
Bis-T-23	Dynamin oligomerization and actin polymerization	Still under trial l (proteinuric kidney diseases, CKD)	–	–

†*Protects synaptopodin from cathepsin L-mediated degradation (stabilizes actin cytoskeleton).*
‡*Potentially ameliorates proteinuria.*
**Reduces uroplasminogen type 1 activator receptor-induced proteinuria/also inhibits angiogenesis.*
***Protects against liposaccharide-induced proteinuria and foot process effacement (adapted from Ref. [68]).*
SRNS, steroid-resistant nephrotic syndrome; CKD, chronic kidney disease; FK 506, nitrogen mustard and tacrolimus; FSGS, focal segmental glomerulosclerosis; TRPC, transient receptor potential cation channel

Table 1.
Summary of current and future treatment targets and the potential drugs for idiopathic nephrotic syndrome.

TRPCs are reportedly expressed, namely, TRPC1, TRPC3, TRPC4, TRPC5, and TRPC6 [56–60]. A striking therapeutic application is the ability of TRPC5 inhibitor (ML204) to protect against lipopolysaccharide (LPS)-induced proteinuria, as well as protamine sulfate- and LPS-triggered foot process effacement [61].

Regarding the supportive function of synaptopodin on the actin cytoskeleton, this protein molecule not only constitutes a linkage to the actin cytoskeleton but remains vital for stress fiber synthesis in podocytes [62, 63]. Despite the previously presumed usefulness of calcineurin inhibitors, like cyclosporine A (CsA) and FK506 in the treatment of INS given their immunosuppressive effects on T cells, the mediatory role of calcineurin on synaptopodin degradation via induction of protease cathepsin L is well established; interestingly, CsA shields synaptopodin from cathepsin L-mediated breakdown, thereby maintaining the integrity of the actin cytoskeleton [64].

Finally, the regulatory activity of endocytic proteins in the actin cytoskeleton is confirmed by recent findings of possible therapeutic benefits of Bis-T-23-induced dynamin oligomerization and actin polymerization for nephrotic syndrome [65]. In fact, some researchers have shown that the GTPase dynamin is important for podocyte physiology [66]. In proteinuric kidney disease, induction of cytoplasmic cathepsin L results in degradation of dynamin, ending up with disruption of the actin cytoskeleton and proteinuria. Again, the modulating effect of dynamin on the actin cytoskeleton is related to the stabilization of the glomerulus. Thus, based on the beneficial activity of Bis-T-23 to kidney health in various models of chronic kidney disease (CKD) through the formation of actin-dependent oligomers of dynamin and polymers of actin, dynamin has been regarded as a possible therapeutic target for the management of CKD [67]. Better still, the recognition of dynamin as one of the vital and autonomous regulators of focal adhesion maturation suggests a molecular mechanism which underpins the beneficial effect of Bis-T-23 on podocyte physiology [67]. The efficacy of some of the therapeutic agents currently used in clinical practice and in experimental animal models is summarized in **Table 1**.

4. Conclusion

Significant progress has now been made in unraveling the complex molecular mechanisms and pathways responsible for maintaining podocyte health and thus the structural and functional integrity of the glomerular filtration barrier. Podocyte injury is now believed to be the basic pathology in childhood INS. As a podocytopathy, disruption of the podocyte architecture eventually results in the massive proteinuria seen in the syndrome. Consequently, several novel therapeutic targets have been proposed and successfully demonstrated, raising hopes for novel pharmacologic agents which could be useful in treating the disorder.

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