INTRODUCTION

Nephrotic syndrome is the most common manifestation of glomerular disease which is characterized by massive proteinuria, hypoalbuminemia, generalized edema and hyperlipidemia [1]. In children, it can be congenital or acquired. Acquired nephrotic syndrome can be idiopathic or secondary; idiopathic nephrotic syndrome (INS) constitutes majority of the cases in children.

The glomerular filtration barrier is basically a trilaminate structure which comprises the glomerular basement membrane (GBM), bounded on the inner layer by fenestrated endothelial lining and wrapped around the outer surface by the podocytes. In most inherited and acquired nephropathies, damage to this glomerular filter is associated with diffuse effacement of the podocyte foot processes [2]. This finding obviously suggests that the podocyte may play a critical role in the pathogenesis of INS, either as a target of a glomerular permeability factor or as the site of disruption of the structure of the foot processes [2]. Thus, the current hypothesis about the pathogenesis of the syndrome is predicated on the alterations at the structural and molecular levels of the podocytes (the concept of a podocytopathy) [3,4]. In fact, all forms of nephrotic syndrome are now thought to be characterized by abnormalities in the podocyte.

The podocyte essentially helps in the maintenance of the glomerular filtration barrier and its structural integrity, as podocyte injury and loss contributes to proteinuria and progressive sclerosis [5]. Podocyte injury can occur in several immunologic and non-immunologic diseases of the kidney; the acquired podocytopathies such as idiopathic minimal change nephropathy (MCN) and focal segmental glomerulosclerosis (FSGS) are considered as immunologic diseases [6]. In these disorders, immunosuppressive agents like steroids and calcineurin inhibitors have been observed to directly affect the podocyte through the regulation of interleukin-4 (IL-4) and interleukin-13 (IL-13) and several signaling pathways which stabilize the actin cytoskeleton, cell maturation and survival, as well as the expression and distribution of key components of the slit diaphragm [5]. For instance, although the effectiveness of steroids in MCN and calcineurin inhibitors in FSGS are well established, the non-immunologic actions of calcineurin...
The therapeutic targets in podocytopathies

Complex molecular pathways help to maintain the integrity of the actin cytoskeleton, and thus the podocyte architecture and function. The healthy podocyte contributes to the intactness of the glomerular barrier. In podocytopathies, alterations in the actin cytoskeleton lead to disruption of this glomerular filtration barrier. The three major molecular pathways which regulate the actin cytoskeleton and circumvent podocyte detachment from GBM include Rho-GTPases, cell-matrix adhesion proteins and endocytic proteins. For example, the Rho family of small GTPases (RhoA, Rac1 and Cdc42) expressed in podocytes, control signal transduction pathways which influence several aspects of cell behavior, including changes in the cytoskeleton [34,35].

The ability of these small Rho GTPase proteins to modulate the actin cytoskeleton suggests their key role not only in the pathogenesis of nephrotic syndrome, but also as potential therapeutic targets [28]. Specifically, the inhibition of small Rho GTPases (RhoA and Rac1) could potentially ameliorate proteinuria, and improve renal function and histological damage [36-39], as increased RhoA activity has been found to result in foot process effacement and clinical manifestation of proteinuria [40]. To corroborate the detrimental effect of RhoA activation on podocyte health, several studies have demonstrated that mice treated with inhibitors for RhoA-dependent kinase (ROCK) reduced proteinuria and prevented renal failure in various murine models of nephropathy [36,37,39,41].

Furthermore, the actin cytoskeleton is also connected to the GBM by a variety of cell-matrix adhesion receptors, including integrins and focal adhesion proteins [28]. The importance of integrins and focal adhesion proteins has been demonstrated in both genetic mouse models of diseases and in human genetic mutations that result in nephrotic syndrome. For instance, α3β1 (the major integrin heterodimer in the podocyte), when both ablated individually in murine podocytes resulted in massive proteinuria and foot process effacement [42,43]. Another key integrin expressed in podocytes is αvβ3 integrin, which can be activated by uroplasminogen type I activator receptor (uPAR) (in podocytes) [44], or its soluble form, suPAR (from the circulation) [45]. The activation of αvβ3 integrin was noted to induce foot process effacement through rearrangement of the actin cytoskeleton [46]. Blocking αvβ3 integrin with an anti-β3 antibody or the small-molecule inhibitor, cilenitide, reportedly reduced suPAR-induced proteinuria: making this integrin a potential therapeutic target [44,45]. In addition, selective pharmacologic inhibition of integrin α2β1 in wild-type mice also attenuated proteinuria [47], while inhibition of key focal adhesion proteins, such as FAK and Crk1/2, reduced podocyte foot process effacement and proteinuria by decreased podocyte migration in murine models of glomerular disease [48,49].

Another potential therapeutic target in proteinuric kidney diseases is themodulating activation of integrin β1 through abatacept (CTLA-4-Ig) or integrin αv inhibitor, cilenitide or integrin α2β1 [44,45,47,50].

The relationship between transient receptor potential cation
channels (TRPCs) and the podocyte actin cytoskeleton has also been well documented [28]. TRPCs are non-selective cationic channels with a predilection for calcium ions, which play a significant role in the pathogenesis of renal and cardiovascular disease [51]. In podocytes, several of these TRPCs have been shown to be expressed; these include TRPC1, TRPC3, TRPC4, TRPC5, and TRPC6 [52-56]. An interesting therapeutic application, for instance, is that TRPC5 inhibitor (ML204) was found to protect against lipopolysaccharide (LPS)-induced proteinuria, as well as foot process effacement induced by LPS and protamine sulfate [57].

With respect to the role of synaptopodin in maintaining the actin cytoskeleton, this proline-rich, actin-associated protein provides a physical linkage to the actin cytoskeleton, and is required for stress fiber formation in podocytes [58,59]. Although the efficacy of calcineurin inhibitors, such as cyclosporine A (CsA) and FK506 (used to treat childhood idiopathic nephrotic syndrome) was originally thought to be due to their immunosuppressive effects on T cells, it has been demonstrated that calcineurin mediates the degradation of synaptopodin by inducing protease cathepsin L. CsA protects synaptopodin from cathepsin L-mediated degradation, thus stabilizing the actin cytoskeleton [60].

Finally, the role of endocytic proteins in regulating the actin cytoskeleton is supported by recent evidence which suggests that Bis-T-23-induced dynamin oligomerization and actin polymerization may have therapeutic implications for the various causes of nephrotic syndrome [61]. Some investigators have shown that the GTPase dynamin is essential for podocyte function [62]. During proteinuric kidney disease, induction of cytoplasmic cathepsin L leads to cleavage of dynamin, leading to reorganization of the actin cytoskeleton and proteinuria. Their study thus identifies dynamin as a key regulator of renal permeability that is specifically targeted by proteolysis under pathological conditions [62]. Furthermore, this physiologic role of dynamin in regulating the actin cytoskeleton has been linked to the maintenance of glomerular filtration barrier. Thus, given the ability of Bis-T-23 to improve renal health in different models of chronic kidney disease (CKD) by promoting actin-dependent dynamin oligomerization and increasing actin polymerization, dynamin has been implicated as a potential therapeutic target for the treatment of CKD [63]. Besides, identification of dynamin as one of the essential and autonomous regulators of focal adhesion maturation points to a molecular mechanism which underlies the beneficial effect of Bis-T-23 on podocyte physiology [63]. In the summary, the side effects and efficacy of some of the therapeutic agents currently used in clinical practice and in experimental animal models are shown in Table 1. For cyclosporine A (a calcineurin inhibitor), its clinical efficacy in cases of steroid-resistant nephrotic syndrome (SRNS) has been proven and documented in several studies [64-66]. In fact, the current KDIGO (kidney diseases: improving global outcomes) guidelines recommend the use cyclosporine A as the first-line option in the treatment of SRNS in children [66]. Although the drug is employed in renal and other organ transplantation, it has been found effective in immune-mediated disorders and nephrotic syndrome. It is preferably combined initially with alternate day steroid (which is tapered off) before converting to monotherapy, during which it can be administered for 12 months or more. Most patients with SRNS remain in remission while on cyclosporine A, or in combination with other immunosuppressive drugs [65]. Its major side effects include tremors, nephrotoxicity, hirsutism, gum hypertrophy, and hypertension.

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**Abbreviations**: †: Protects Synaptopodin from Cathepsin L-Mediated Degradation (Stabilizes Actin Cytoskeleton); 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; ‡: Potentially Ameliorates Proteinuria; *: Reduces Uroplasminogen Type 1 Activator Receptor-Induced Proteinuria/also Inhibits Angiogenesis; **: Protects Against Lipopolysaccharide-Induced Proteinuria and Foot Process Effacement
CONCLUSIONS

Podocyte pathology is now considered as the conventional paradigm to explain the pathogenesis of nephrotic syndrome. Much progress has been made in understanding the intricate molecular mechanisms and pathways responsible for maintaining podocyte health, and thus the integrity of the glomerular filtration barrier. Sequel to these advances on disease pathogenesis, several novel therapeutic targets have been hypothesized and successfully demonstrated, raising hopes for further discoveries of pharmacologic agents for the treatment of nephrotic syndrome. Previous therapies for the syndrome have focused on modulating the immune system with the use of immunosuppressive drugs such as glucocorticoids and cytotoxic drugs. Specifically, calcineurin inhibitors such as cyclosporine A (in combination with alternate day prednisolone) has been found effective in inducing remission in 60-70 percent of patients with SRNS and in about 30-40 percent of those with focal segmental glomerulosclerosis (FSGS). Thus, among these pharmacologic agents with potential actions on podocyte physiology and pathology, cyclosporine A is the best regimen and the most recommended drug for use in SRNS despite its cost and side effects. However, before routine clinical application could be achieved in the rest of the therapeutic agents, these novel discoveries need final validation with randomized controlled trials.

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