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Review Article

Podocytes as a therapeutic target

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Abstract

A glomerulus is the filtration unit of a kidney where its primary function is to filter the blood and produce urine. The filtration apparatus of a glomerulus is composed of a three layered cellular assembly that consists of endothelial cells, GBM (glomerular basement membrane) and epithelial cells known as podocytes with their specialized junctions commonly known as the "slit diaphragm", or the filtration slits. Injury to podocytes has been shown as a common denominator in various glomerular diseases leading to ESRD (end stage renal diseases) and renal failure. The podocytes have a unique architecture that is composed of a podocyte cell body and primary and tertiary processes that are critical for podocyte function. Podocytes lose their unique structure in the event of a glomerular injury, which is most often associated with podocyte actin cytoskeleton damage and podocytes detachment from the GBM leading to the loss of renal function. Studies over the past decade have established podocytes as a cell type critical for glomerular function, thus making them an ideal therapeutic target to develop therapies directed towards preserving glomerular filtration function. Recent studies have highlighted several cellular mechanisms and signaling targets such as suPAR, PLA2R, Rac1, Crk1/2, Trpc5, mTOR, Trpc6 and Notch that are involved in regulating podocyte function. More importantly, these studies have fueled the recent discoveries aimed at the identification and development of novel therapies or agents with the ability to preserve podocyte structure and function. The present review is an attempt to summarize the recent discoveries that have been made in the field of podocyte therapeutics and their impact on podocyte biology.

INTRODUCTION

The filtration system of a kidney is critical for retaining essential proteins from the blood plasma and removal of toxic waste from the body. When a kidney loses its filtration function it results in life threatening complications and the survival usually depends on dialysis and eventually surgical intervention requiring a kidney transplant. The filtration function in a kidney is carried out by glomeruli and each glomerulus with its tubules is termed as a "nephron" which is also known as the filtration unit of the kidney [1]. A human kidney is composed of approximately 1 million glomeruli and on an average filters about 200 quarts of blood plasma generating about 2 quarts of urine per day [2]. The filtration function of a glomerulus is affected by a wide spectrum of diseases such as FSGS (focal and segmental glomerulosclerosis) and various nephrotic syndromes that are also the leading causes of end-stage renal disease (ESRD) [3-5]. The incidence of ESRD is increasing at an alarming rate and costs about $49 billion a year in patient care [6,7]. Limited progress has been made in the therapeutic advancement in this field primarily due to poor understanding of the basic mechanisms that regulate the different layers of the filtration assembly of the glomerulus.

The filtration barrier of a glomerulus is composed of three major cellular layers, the fenestrated endothelium, the intervening glomerular basement membrane (GBM) and podocytes, which collectively contribute towards the selective ultrafiltration of the blood plasma (Figure 1) [8,9]. This three layered structure facilitates the flow of plasma water and small solutes while restricting the flow of large plasma proteins such as albumin. Increased amount of albumin in the urine is the primary indication of a defective glomerular filtration barrier, a condition commonly known as "proteinuria" or "albuniuria". Various glomerular diseases that induce proteinuria also demonstrate significant structural damage to podocytes [3,5,10]. These changes in podocytes have become the hallmark of proteinuria and serve as the diagnostic marker for various glomerular diseases [3,8]. This has also resulted in the worldwide acknowledgement of podocytes as the primary target for developing therapies against the existing glomerular diseases [11-13]. A significant effort is being made worldwide to understand the underlying mechanisms that regulate the structural and functional development of podocytes [14-16]. The past decade has seen a tremendous progress in the field of glomerular biology where a number of biomolecules and pathways have been uncovered that play a critical role in the maintenance of the filtration function of this filtration barrier [11,17,18] (Figure 1). Furthermore, it

is critical that we understand the assembly and maintenance of this structure that will contribute towards designing novel therapies towards the prevention of this structure in the event of a glomerular injury (Figure 1).

Podocytes organization and the slit-diaphragm

The podocytes are highly specialized epithelial cells that consist of a cell body that branch off to give primary, secondary and tertiary processes. The tertiary processes also known as "foot processes" are attached to the GBM and extend as finger like projections that surround the glomerular capillary in an interdigitating fashion with the cell body facing the Bowman's capsule and the urinary space [19]. The podocytes are highly polarized cells with apical or luminal and a basal cell membrane domain. The basal membrane, which contains the sole of foot process, is affixed to the GBM. The surface of the apical membrane is negatively charged because of its composition that contains sialoglycoproteins such as podoclyxin and podoendin [20]. Both apical and basal membranes are heterogeneous in nature with respect to their lipid composition [21,22]. Foot processes from different cell bodies interdigitate and the spaces between adjacent foot processes are connected via a thin membranous structure that is 40nm wide and is commonly known as the filtration slit or "slit-diaphragm" [3,5]. The unique structural organization of the slit diaphragm has been proposed to function as a permeability barrier, where it is freely permeable to water and small solutes and restricts the passage of large molecules such as albumin [3,23]. Several research findings reveal that proteins localized at the slit diaphragm play a critical role in maintaining the structure and function of podocytes [3,5,24]. Extensive research in this field has identified transmembrane proteins including Nephrin, Neph1, podocin, FAT and P-Cadherin that serves as the building blocks for this fascinating structure [3,5,10]. The cytoplasmic domains of Nephrin and Neph1

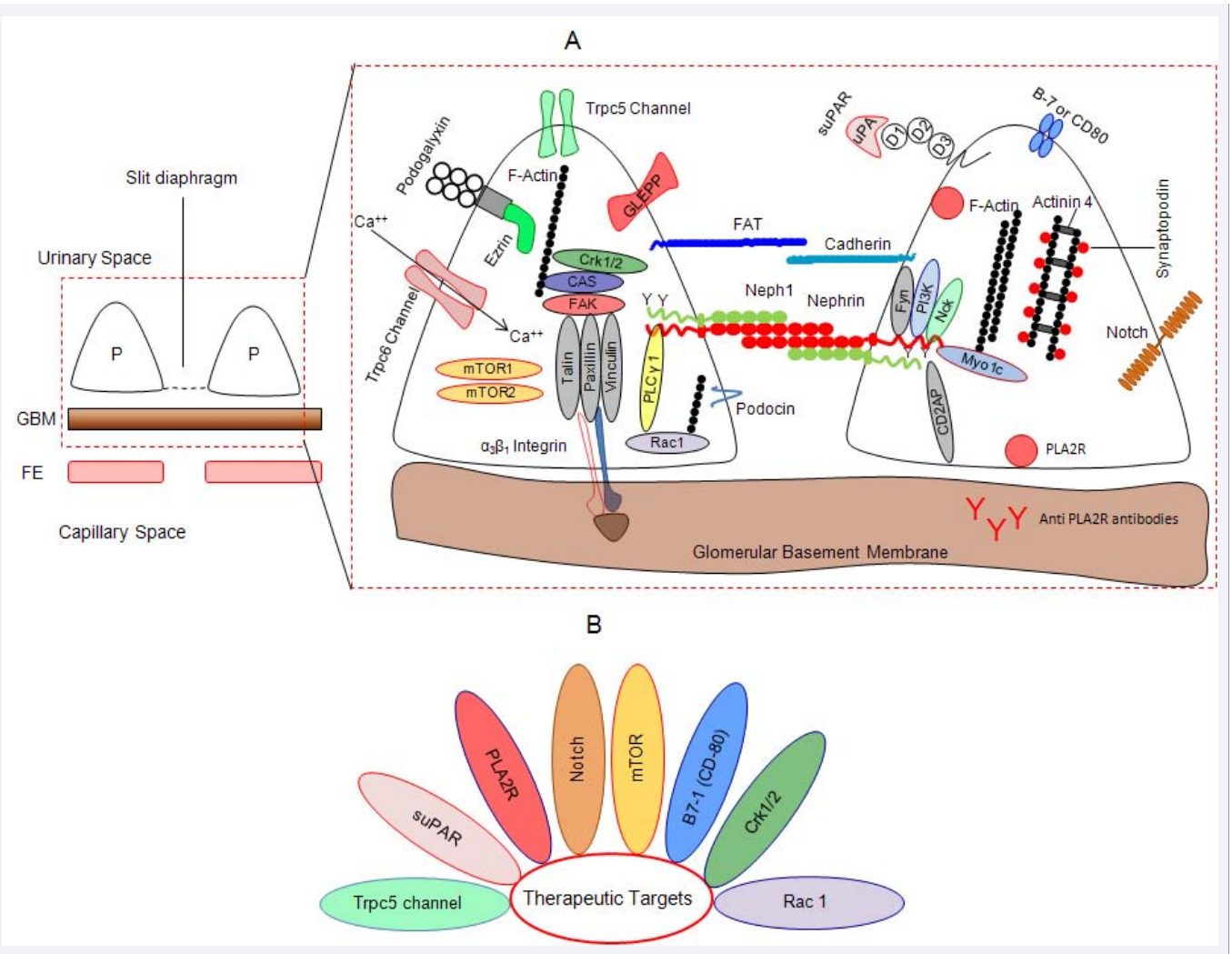

Figure 1 (A) The schematic representation of the glomerular filtration assembly. The Glomerular filtration barrier is composed of fenestrated endothelium (FE), glomerular basement membrane (GBM), podocytes (P) and their specialized junctions known as the slit-diaphragm. Podocytes slit diaphragm is a dynamic structure that originates as the junction between two adjacent foot processes. The glomerular diseases induce injury to podocytes leading to the loss of slit diaphragm that is strongly associated with leakage of protein in urine and loss of renal function. Ultrastructural analysis of this structure shows the presence of various proteins including Nephrin and Neph1 whose extracellular domains provide the structural framework of slit diaphragm and the intracellular domains assemble key signaling pathways that regulate the integrity of this structure. (B) A number of these pathways are being recognized as therapeutic targets for developing therapies to prevent podocyte damage.

have been shown to serve as a structural link between the slit diaphragm and the actin cytoskeleton of podocytes and therefore were shown to participate in the signaling events that regulate the overall structure and function of podocytes [3,23]. Apart from these, several adapters, signaling and motor proteins including zona occludens-1 (ZO-1), CD2 adaptor protein (CD2AP), Nck, Crk 1, 2 and 3, Myo1c and Myo1e have also been identified that together contribute to the maintenance and integrity of the slit diaphragm [25-30]. Inactivation or genetic deletion of these proteins has been shown to induce structural alterations in podocytes leading to podocyte dysfunction and proteinuria in mice; more importantly, various glomerular diseases in humans have been shown to be linked to genetic mutations in many of these proteins [3,5,15,19,31], which further substantiates the role of these proteins in glomerular biology [23,32,33].

Podocyte injury

Podocyte injury is the common denominator in many forms of human and experimental glomerular diseases such as minimal change disease, focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy, diabetic nephropathy (DN), and lupus nephritis [2,4]. Numerous studies now suggest that the injury to podocytes is the direct leading cause of glomerular disease development particularly in the case of FSGS [34-36]. Most notably, using various animal models it has been demonstrated that podocytes are the most vulnerable components of the glomerular tuft and that in majority of FSGS cases, it is the injury to podocytes that initiates the definitive pathologic sequence [37]. Podocytes are severely limited in their ability to repair themselves and are unable to replicate postnatally as suggested by the lack of an increase in podocyte cell number postnatally and during compensatory growth [34,38,39]. Data from the podocyte cell culture studies suggest that the differentiated podocytes are unable to proliferate, whereas undifferentiated or dedifferentiated podocytes from isolated glomeruli can proliferate [40-42]. An experimental animal model suggested that podocytes subjected to sustained mitogenic stimulation by FGF-2 [43] entered the cell cycle but were unable to reach the complete cell division, and resulted in bi- or multinucleated podocytes. Multinucleated podocytes were also observed in studies involving experimental [38,44] and human glumerulopathies [45-47]. Additionally, the loss of differentiated podocytes markers GLEPP1, synaptopodin, C3b-receptor and the transcription factor WT-1 expression was noted in these models [48]. These studies highlight the need for developing therapeutic alternatives that are directed towards preserving podocyte loss in the event of a glomerular injury.

Several studies of podocyte injury models note that early podocyte injury can be reversible where the actin cytoskeleton of podocytes has the ability to reorganize and restore the unique podocyte morphology [49-51]. Based on the nature of an injury, there are two models of podocyte injury, characterized as either chronic or acute; however, both lead to the loss of normal podocyte architecture and progression towards ESRD [50-52]. Additionally, there are different pathways including a dysregulated, inflammatory pathway, and a degenerative pathway that is proposed to function in podocyte injury [14,53]. In a dysregulated pathway that is commonly seen in the case of HIV-associated nephropathy, the dedifferentiation of podocytes leads to podocyte proliferation within Bowman's space, collapsing of the glomerular tuft, GBM wrinkling and capillary loss [53,54]. The inflammatory pathway can lead to podocytes fixation to the parietal basement membrane followed by the establishment of tuft adhesions to Bowman's capsule [53]. Further proliferation of podocytes and parietal cells results in the formation of cellular crescents and the healing of lesions by fibrosis results in segmental glomerulosclerosis [53]. In the case of degenerative form, which is most commonly observed, the persistent podocyte injury causes cell body attenuation, podocyte hypertrophy, and detachment from the GBM, and podocyte death leading to glomerulosclerosis and loss of renal function [53,54].

The Podocyte pathological lesion is also of common occurrence in other glomerular diseases such as inflammatory diseases (glomerulonephritis), immune-mediated diseases (membranous nephropathy, Heymann nephritis), mechanical stress (glomerular hypertension) and animal models of PAN (puromycin aminonucleoside) treatment. The Podocyte lesions may develop because of direct injury to podocytes, detachment of podocytes from the GBM or the damage of GBM [55,56]. Among the various animal models of podocyte injury developed over the years, the two models that have gained widespread recognition are the rat model of PAN injury where injury is induced by the administration of PAN and the protamine sulphate mouse model where podocyte damage occurs in response to the infusion of a highly cationic compound [26,49,57-59]. Importantly, these models have also been replicated in the podocyte cell culture system and thus have served as an excellent source to demonstrate cytoskeletal and molecular changes in podocytes and identify the various pathways that are affected during injury to podocytes [60-62].

An alternate mechanism of podocyte injury was noted in the study of integrins that play a central role in the attachment of podocytes to the GBM [63-65]. The antibodies directed against the antigens present in the basal podocyte cell membrane such as gp330 [66-68] or dipeptidylpeptidase IV [68] were shown to affect α3β1 integrin-fibronectin/laminin interactions leading to podocyte detachment from GBM and podocyte damage [37,65]. Furthermore, the genetic inactivation of α3 or β1 integrins was shown to induce severe disorganization of podocyte foot processes (FP) and loss of kidney function in newborn mice [69]. Damage to the GBM itself has been observed in various inflammatory and immune-mediated diseases where the injury is induced by reactive oxygen species (ROS) from neutrophils, monocytes/macrophages or resident glomerular cells that attack the GBM, or direct oxidation of GBM and by the activity of proteases that degrade the GBM or the connection of podocytes with the GBM [64,65,70-76]. Collectively, these studies highlight several mechanisms that contribute towards the podocyte injury and thus present multiple targets in podocytes that can be exploited therapeutically.

Molecular changes in an injured podocyte

The actin cytoskeleton of podocytes contributes towards the structural framework, unique morphology and maintaining the podocyte cell body and the function of podocytes. This actin cytoskeleton is divided into two major groups, the longitudinal actin microfilaments and the meshwork of actin filaments beneath

the cell membrane [24,51,77]. The cytoskeleton of the primary podocyte FPs is composed of microtubules that in addition to providing structural support to the cell, anchors the intracellular molecules and impart the contraction and expansion abilities to the cells [23,24]. The FPs are also characterized by the cortical network of short branched actin filaments and the presence of highly ordered parallel, contractile actin filament bundles, which are thought to modulate the permeability of the filtration barrier through changes in foot process morphology [24,51,77]. Apart from the structural stability the actin cytoskeleton plays a major role in cell signaling and the intracellular organization of podocyte proteins [15,32,51,52]. The disorganization of this well characterized podocyte actin cytoskeleton is a major event evidenced during podocyte injury [11,51,52,78]. These changes often lead to flattening of podocytes that is commonly referred to as "podocyte effacement" and loss of the slit diaphragm [14,26,37]. Over the years several actin associated proteins including actinin-4 and synaptopodin that regulate the dynamics of actin cytoskeleton have been investigated. Genetic mutations of Alpha-Actinin-4 in human and knockout or over expression have been associated with the development of glomerular diseases leading to proteinuria [79-81]. Analysis of synaptopodin-null mice showed that these mice were resistant to protamine sulfate induced foot process effacement synaptopodin suggesting a critical role for synaptopodin in podocyte biology [81]. Additionally, actin based molecular motors such as Myo1c and Myo1e that are associated with protein trafficking has been recently investigated for their role in podocyte development, maintenance and glomerular function [25,29,82,83]. Growth factor receptors such as vascular endothelial growth factor [84,85] and transforming growth factor β [70], GPCRs such as the angiotensin type 1 receptor (AT1R) [86,87], signaling through Notch [88,71] or integrins [89-92], TRPC ion channels such [93,72,73], suPAR [74], PLA2R [94] and many other molecules have been identified for their role in podocyte injury.

The increasing evidence now overwhelmingly suggests that maintaining a healthy actin cytoskeleton is central to podocyte maintenance and function and therefore, targeting the well being of podocyte actin cytoskeleton is a reasonable therapeutic approach to prevent podocyte function in the event of a glomerular injury.

Podocytes as therapeutic target

With the growing incidences of glomerular diseases worldwide, there is an urgent need for better therapies that are directed towards preserving podocyte function and reduce the morbidity and mortality rates associated with renal failure. Recent advancements in the drug therapy field has led to the identification of many drugs including glucocorticosteroids and calcineurin antagonists with observed potent protective effects; however, the nonspecific nature of these drugs with undesirable systemic adverse effects severely limits their potential use and suggests the need for further research to uncover novel therapeutic alternatives to prevent podocyte damage [11]. Among the podocyte targets, angiotensin inhibition has gained significant attention due to its ability to prevent the development of glomerulosclerosis in animal and cell culture models [95,96,75]. The soluble form of the urokinase plasminogen-activator receptor (suPAR) that was earlier investigated for its possible role in cell motility, invasion and metastasis was recently characterized as the FSGS inducing factor and was shown to be elevated in the FSGS patients [74,97]. This finding has galvanized the podocyte community and has led to the designing of therapies directed towards lowering the suPAR levels in blood plasma [74,97].

Among the other pathways, the transmembrane receptor, M-type phospholipase A2 receptor (PLA2R), has been identified as a target antigen in membranous nephropathy [76,98] The glomerular PLA2R expression was elevated in the MN patients that contained increased anti-PLA2R antibody levels as compared to the MN patients without detectable anti-PLA2R antibodies or patients with other types of glomerular diseases [99]. The PLA2R expression can be assessed in kidney biopsies and differentiates patients with MN caused due to anti-PLA2R antibodies from those with secondary forms of MN. The Rituximab-Induced depletion of Anti-PLA_2R autoantibodies has emerged as a promising therapy for MN patients; however, some patients entered into remission following this therapy [100], which further suggests that further investment should be made in understanding the pathogenesis of this disease and designing alternate therapies.

Molecular targets in podocytes

It is of no big surprise that many investigators are recognizing the potential of podocytes as therapeutic targets and are targeting pathways specifically within the podocytes to develop therapies for preserving glomerular filtration function. Some of the most promising strategies include targeting the B7 protein and the TRPC (transient receptor potential) channels [93,101]. A recent study suggested that the expression of B7-1 (CD-80) protein was elevated in certain glomerular disease conditions [101]. The B7-1 promotes disease-associated podocyte migration through inactivation of β1 integrin and hence the B7-1–positive podocytes demonstrate reduced ability to attach to the surrounding matrix through β1 integrin. The increased B7-1 protein expression is associated with increased podocyte migration, which serves as a marker for podocyte effacement and proteinuria [101]. Remarkably, Abatacept (CTLA-4–Ig) a known inhibitor of the T-cell co-stimulatory molecule CD80 appears to cure the nephrotic syndrome patients that were shown to contain increased levels of B7-1 protein [101].

The other major pathway that recently gained significant attention for its therapeutic value involves TRP channels. The TRP channels are highly conserved nonselective cationic channels, and play a major role in chemo and mechanosensation [93,101]. The TRPC6 channel was shown to be a functional component of podocytes where it was investigated for its interaction with scaffolding molecules, signaling proteins, cytoskeletal elements, and many ion channels such as Ca^{2+}-activated K^+ channels (BK_{Ca} channels) [93,101]. Alteration in the function of this ion channel was shown to be associated with podocyte damage suggesting its role in maintaining glomerular function [93,102,103]. Moreover, gain of function mutations in TRPC6 in humans or the overexpression of the wild-type TRPC6 protein in mice both induced renal damage [104,105]. Although TRPC6 is expressed in many cells types but mutation of TRPC6 primarily demonstrated FSGS like symptoms and did not produce any other pathological phenotype [106]. This unique glomerular phenotype suggests the

exceptional role of TRPC6 in podocytes that may regulate subtle changes in Ca^{2+} dynamics and actin cytoskeleton [106,107]. These studies have led to multiple experimental hypotheses, which focus on modifying TRPC6 expression or blocking TRPC6 channels using specific inhibitors as potential therapeutic strategies [90,107]. Another TRP channel, the TRPC5 that is highly expressed in brain and kidney was recently shown to be an essential component of the glomerular filtration system [108,109]. The TRPC5 and TRPC6 channels act as antagonistic regulators of actin remodeling and cell motility in fibroblasts and kidney podocytes [72]. Recent study revealed that loss of TRPC5 in mice or the pharmacological inhibition of TRPC5 by a small molecule inhibitor prevented the activation of small GTP binding protein Rac 1 and stabilized Synaptopodin and protected mice from albuminuria [109].

Cell signaling as a potential target in podocyte

The Rho-family small GTPase including RhoA and Rac1 are associated with cellular signaling, cell migration and inflammation in a variety of cell types [110,111]. Activation of these molecules has been associated with podocyte injury and proteinuric kidney disease [110,111]. The role of small GTPases has been implicated in dynamic shape changes seen in podocytes during development and in disease states [51]. The GTPase Cdc42 has been shown to play a role in the podocyte development, whereas, RhoA and Rac1 GTPases are seems to be involved in post development stages of podocyte maintenance [112]. The Activation of RhoA or the overexpression of dominant negative RhoA resulted in foot process effacement and proteinuria [113,114]. In contrast, the podocyte-specific loss of Rac1 protected mice from the glomerular injury induced by protamine sulfate infusion [115]. Further the rac1 inhibitors were found to inhibit the increased Rac1 and CDC42 dependent cell migration observed in steroid resistant nephrotic syndrome (NS) [116]. Additionally, the podocyte-specific, inducible transgenic mice expressing constitutively active Rac1 lead to the rapid onset of proteinuria and foot process effacement [112]. Collectively, these findings provide ample evidence for the role of GTPases in regulating podocyte structure and function and thus modulating their function has become a novel approach in developing therapies for the treatment of chronic kidney diseases [112].

A recent report highlighted the role of another signaling protein Crk and its family members (Crk1/2 and CrkL) that were shown to interact with the slit diaphragm protein nephrin [26,32]. Crk plays a pivotal role in transducing signals that regulate actin cytoskeletal dynamics, cell spreading, and motility by mobilizing and activating Rho family of small GTPases, [117-119]. Crk-mediated signaling can be initiated by a variety of stimuli including growth factors, cytokines, or integrin-mediated cell adhesion, and is involved in cell proliferation, differentiation, and cell motility [119]. Interestingly, the podocyte specific deletion of Crk1/2 in mice prevented foot process effacement in a podocyte injury model where the injury was induced by the infusion of protamine sulfate [26]. It is notable that Crk mediates its function through FAK (focal adhesion kinase) and Cas protein complex which were also hyper-phosphorylated in the glomeruli of minimal change disease and membranous nephropathy patients [26]. This study was remarkable in the sense that it provided FAK as a novel therapeutic target in podocytes [26]. Indeed, genetic and pharmacological inactivation of FAK was shown to attenuate the foot process effacement and proteinuria in various diseased models [120]. Although these studies have shown promising targets for preventing podocyte damage in response to glomerular injury, they may only target a subset of glomerular diseases [26]. Therefore, future studies should be considered to evaluate such inhibitors in specific susceptible subsets of human glomerulopathy in which podocyte FAK and Cas are phosphorylated.

Activation of Notch pathway plays critical role in the development of a kidney and the pathogenesis of glomerular diseases [71,121]. Four Notch receptors exist in mammals that are activated upon the binding of ligands such as Delta-like1, 3, and 4, and Jagged 1 and 2 leading to a series of proteolytic steps initiated by presenilin-dependent gamma secretase-like protease [122]. This results in the release of Notch intracellular (IC) domain, which ultimately translocates to the nucleus and binds RBP-jk transcription factor and activate the expression of Notch effector protein [122,123]. While Notch signaling is required during nephrogenesis, its suppression is necessary for differentiation [124-127]. The upregulation of Notch signaling has been identified in many kidney diseases including inflammation and fibrosis, and during glomerular injuries such as immunodeficiency virus-associated nephropathy (HIVAN) [121,122,128,129]. It was further established that the activation of Notch pathway specifically in podocytes was sufficient to induce podocyte loss and glomerular failure. In contrast, the genetic ablation of Notch pathway resulted in resistance to podocyte apoptosis and albuminuria [71]. Interestingly, γ-secretase inhibitors also prevented disease onset in a toxic podocyte damage model, further supporting Notch signaling as a therapeutic target for preventing podocyte damage [130].

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase of the phosphoinositide 3-kinase (PI3K)-related kinase family that contains two distinct complexes, mTORC1 and mTORC2. Rapamycin is a fungal metabolite that is known for its potent growth-inhibitory and immunosuppressant functions [131,132]. The mTORC1 is mainly involved in regulating cell cycle progression, translational control, and cellular energy responses [133], whereas mTORC2 was identified as the kinase responsible for phosphorylating Akt and plays a major role in regulating actin cytoskeleton [134,135]. Role of mTOR has been investigated in various human diseases including cancer, diabetes, neurodegenerative disorders, and polycystic kidney disease [136,137]. Recent investigations revealed that inhibition of mTORC1 by rapamycin or everolimus can favorably modify glomerular diseases, such as minimal change disease [138], focal segmental glomerulosclerosis [139], membranous nephropathy [140,141], crescentic glomerulonephritis [142], and diabetic nephropathy [143]. Studies also suggest that mTOR inhibiton can protect and prevent podocytes from progressive diabetic nephropathy [144]. In diabetic animals, rapamycin prevented GBM thickening, glomerular hypertrophy, mesangial expansion, and renal macrophage [143]. Despite the protective effect of rapamycin in animal models the use of rapamycin therapy in human patients has been limited due to a varied human response possible due to off-target effects of rapamycin [145]. This

further suggests a need for better in-depth understanding of this pathway and its functional role in various glomerular diseases. Nevertheless, development of drugs that have the potential to modify this pathway will be promising future therapeutic candidates for the treatment of glomerular diseases.

It is remarkable, yet baffling that the proteins that are so essential for podocyte function, their loss (rather than being detrimental for podocyte function), protects podocytes from injury [26,101,109,112] (Figure 1). There are two possible hypothetical explanations for such occurrence; either the protein loss has a differential response based on the nature of the glomerular disease and thus may offer protection in one model but may aggravate disease in other models or the loss of protein shuts of the signaling pathway that is involved in the injury response and thus rendering the cell unresponsive to the injury stimulus. Genetic deletion of Rac1 provides support for the first hypothesis since it showed protective effect in the protamine sulphate injury model and had aggravated injury response in the long-term model of chronic hypertensive glomerular damage [112]. Since these signaling proteins mediate a broad range of biological processes and are involved in numerous pathways, further studies are necessary to identify additional downstream or upstream signaling targets that will aid in designing specific and highly effective therapies for restoring glomerular function during renal injury.

CONCLUSIONS

Preventing podpocyte damage will prevent glomerular injury and preserve renal function, is soon becoming the mantra of the podocyte biologists. This is largely due to our increased understanding of the podocyte biology in the last decade. Additionally this has significantly contributed towards the identification of molecular targets with applications in glomerular disease prevention and progression. Understanding of the signaling pathways in podocytes have taught us that podocytes are regulated through complex set of mechanisms and therefore, therapeutic advancement in the field of podocyte biology will require multiple approaches to identify multiple targets and develop combinatorial therapies to prevent podocyte damage and thus preserve renal function. With the increasing knowledge of the molecular composition of podocytes, the investigators in the field of podocyte biology are uniquely positioned to identify several druggable targets that will aid in the development of therapies directed towards preventing podocytopathy.

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