Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.23.003919

Actin Cytoskeleton Stabilization of Kidney Podocyte and Proteinuria

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ARTICLE INFO

Received: November 27, 2019

Published: December 04, 2019

Citation: Mengjun Liang, Xing Zhang, Zongpei Jiang. Actin Cytoskeleton Stabilization of Kidney Podocyte and Proteinuria. Biomed J Sci & Tech Res 23(3)-2019. BJSTR. MS.ID.003919.

Keywords: Proteinuria; Podocyte; Synaptopodin; Calcineurin; TRPC6

Abbreviations: CNIs: Calcineurin Inhibitors; MCD: Minimal Change Disease; FSGS: Focal Segmental Glomerulosclerosis; LN: Lupus Nephritis; GBM: Glomerular Basement Membrane; CIRB: Calmodulin and IP3 Receptor-Binding; PLC: Phospholipase C; DAG: Diacylglycerol

ABSTRACT

Objective: Proteinuria is an important sign and the key therapeutic target for glomerulonephritis. Based on the remarkable effect of Calcineurin inhibitors (as CyclosporinA) in massive proteinuria caused by focal segmental glomerulosclerosis or membranous nephropathy that is thought to be podocytopathy, we planned to conceive a brief review to ravel out the relationship between proteinuria and podocyte cytoskeleton.

Method: All references were selected from PubMed within latest ten years. The search key words contained proteinuria, podocyte, synaptopodin and calcineurin.

Results & Conclusion: Current studies have indicated that cytoskeleton stabilization of kidney podocyte plays an important role in development of proteinuria. Synaptopodin is a key stabilizer of actin cytoskeleton in podocyte through forming Synaptopodin-p-β-14-3-3 protein complex. Serine/threonine protein phosphatases, as calcineurin, can abrogate the Synaptopodin-p-β-14-3-3 interaction and prompt Synaptopodin hydrolysis causing disruption of cytoskeleton. Calcineurin, silent normally, will be activated by increment in cytosolic Ca^{2+} concentration which is mainly related to mutation of transient receptor potential channel-6 (TRPC6) locating in cytomembrane of podocyte. TRPC6 abnormality, Ca^{2+} influx and Calcineurin activation may also induce podocyte apoptosis. Furthermore, researchers have confirmed some new podocyte-related mechanisms for the classical therapy of proteinuria, including glucocorticoid receptors present in podocyte, Calcineurin-Synaptopodin inhibitors and TRPC6-Calcineurin pathway hinders. Therefore, all these evidences suggest that modulation of actin cytoskeleton in podocytes is closely associated with progress of kidney diseases especially proteinuria.

Introduction

The mechanism of proteinuria is a hotspot for kidney disease research. Proteinuria is an important sign of glomerulonephritis and is an independent risk factor for kidney disease progression. Proteinuria resulting from the increased permeability of glomerular capillary, may be linked to the inflammatory response of immune system; [1] therefore, corticosteroids and immunosuppressants are widely used for treatment of glomerular disease. Recently, more clinical studies have confirmed that Calcineurin inhibitors (CNIs) have effect on both primary and secondary glomerulonephritis, such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and lupus nephritis (LN) [2-4]. However, it's equally effective for genetic glomerular disease like Alport syndrome [5]. The study by Faul C showed that Cyclosporin A reduces proteinuria by maintaining stabilization of podocytal actin cytoskeleton, leading a new way to elucidate the effect mechanism of CNIs [6]. This article is to review the mechanism of actin cytoskeleton stabilization of podocytes and development of proteinuria, to provide a theoretical basis for clinical practice.

Molecular Basis of Glomerular Filtration Barrier

Glomerular is composed of rich and highly specific capillary bed, selectively filtering plasma substances. Filtration barrier includes three sections, capillary endothelial cells, glomerular basement membrane (GBM) and epithelial cells (podocytes). Podocytes, locating outside the GBM, include cell body and foot processes. The thin membrane structure between the podocyte foot

processes is called slit diaphragm, on which some certain proteins, including Nephrin and Podocin can be used as signal transduction molecules to regulate podocyte cytoskeleton. Slit diaphragm can effectively prevent the loss of useful substances and proteins in plasma. Recent studies show that passage of albumin across the glomerular filtration barrier is not only driven by the two widely known effects: diffusion caused by concentration difference and convection caused by water pressure difference but associated with electrical effects caused by potential difference. Plasma is rich in Na^+, K^+, Cl^-, and HCO_3^-. During filtration, the cations interact with negatively charged filtration barrier, while the anions can quickly enter the Bowman's space. The resulting potential difference can make filtered-out protein return to plasma. Menzel S noted that podocytes constitute electric resistance of the filtration barrier and is the main structure to form potential difference [7]. So, podocyte is the critical component in this highly complicated filtration system.

Synaptopodin and Calcineurin in podocyte

Podocyte is a terminally differentiated cell, of which stability depends on the actin cytoskeleton. Synaptopodin is an actin-binding protein and a key stabilizer of the actin cytoskeleton in podocytes. Synaptopodin contains two consensus binding motifs, amino acids 212-218: RAAATTP and amino acids 615-621: RPSRSSP. When Thr216 and Ser619 are phosphorylated (RAAApTTP and RPSRpSSP respectively) under serine/threonine protein kinases including protein kinase A (PKA) and calcium-dependent protein kinase II (CaMKII), Synaptopodin will combine to β-14-3-3 proteins within podocytes, forming Synaptopodin-p-β-14-3-3 protein complex, which maintains cytoskeleton stability [6]. Serine/threonine protein phosphatases in podocyte, as Calcineurin, can abrogate the Synaptopodin-p-β-14-3-3 interaction and make it easier to be hydrolyzed by CathepsinL (Cat-L). Calcineurin is silent normally, while increment of cytosolic Ca^{2+} concentration would up-regulate its activation. Mutations of channel proteins locating on podocyte can increase cytosolic Ca^{2+} concentration and activates Calcineurin, promoting the hydrolysis of cytoskeletal proteins. The most important one is transient receptor potential channel-6 (TRPC6) [8].

Structure and Modulation of TRPC6

TRPC channel proteins are widely present in vertebrate animals, and the human TRPC family has six subtypes (TRPC1-6). In kidney, TRPC6 is mainly distributed in the podocyte and slit diaphragm, while thinly distributed in the glomerular capillary endothelial cells, mesangial cells and collecting tubule epithelium. TRPC channels are tetrameric proteins composed of six transmembrane segments, a pore-forming region between the membrane segments 5 and 6, and with NH2 and COOH termini facing the cytosol. Four ankyrin repeats (Ank 1-4) and one coiled-coil domain are present in the NH2-termini, with a coiled-coil domain, a calmodulin and IP_3 receptor-binding region (CIRB region), and a highly conserved proline-rich sequence TRP domain in the COOH-termini. Interaction sites with other molecules and the mutation ones are known to involve both NH2 and COOH termini. Activation of TRPC6 causes Na^+ and Ca^{2+} influx. In the initial stage, Ca^{2+} influx can cause coordinated activation of BKCa by binding to Ca^{2+}-binding domains in the subunits of BKCa channels (Slo1 proteins) which is colocalizated with TRPC6.7 Activate BKCa channel causes K^+ efflux, antagonistic to membrane depolarization caused by Na^+ influx, thereby forming the continued influx of Ca^{2+} through TRPC6 channel. Change of lipid environment is the most important way to activate TRPC6 channel, for example, phospholipase C (PLC)-diacylglycerol (DAG) mediating lipid exchange, phosphorylation pathway in Nephrin and Podocin [9].

Abnormalities of TRPC6 and proteinuria

Abnormalities of TRPC6 in kidney diseases include two conditions, mutation of TRPC6 protein found in podocytes of patients with hereditary FSGS; [10] and increasing normal TRPC6 found in patients with some acute acquired renal diseases [11,12]. Early studies of hereditary FSGS indicated the main mutations of TRPC6 include Six N-terminal missense mutations (G109S, P112Q, M132T, N125S, N143S, and S270T) locating around ankyrin repeats; C-terminal mutation locating in TRP channels contain L780P, K874*, Q889K, R895C, and E897K, involving changes in coiled-coil domain [13]. Ank is the key functional unit of TRPC proteins, related to homologous or heterologous oligomers between TRPC proteins, and its mutation may affect TRPC6 transmembrane sites insertion, then cause abnormal TRPC proteins present on cell surface. The mutation P112Q significantly raises channel density at the plasma membrane. The mutation N143S and S270T allow channels to stay open longer. The mutation M132T causes a mean inward calcium current 10-fold larger than normal, related to childhood FSGS. The coiled-coil domain at the C-termini is commonly used for oligomerization. Meanwhile, El Hindi S reported that the mutation R895C and E897K result in TRPC6 channels with higher current amplitudes [11].

These phenomena suggest that abnormalities of TRPC6 protein during both anchoring and oligomerization process will affect its activity. El Hindi S and his group also found that, in patients with membranous nephropathy, complement C5b-9 complexes depositing on podocyte could result in significant increase of the number of normal TRPC6 on cytomembrane through activating intracellular PLC [11]. Many humoral factors can activate PLC inside podocytes, such as angiotensin, high sugar, prostaglandin E2 and atrial natriuretic peptide, etc. Besides, the absence of Nephrin as shown in neonatal $Nephrin^{-/-}$ mice led to increased expression of TRPC6 in podocytes with particles-aggregation-like distribution, suggesting the absence of Nephrin induces changes in expression and distribution of TRPC6 [9]. When TRPC6 is activated, surge of Ca^{2+} influx causes activation of Calcineurin, which dephosphorylates Synaptopodin and results in Synaptopodin hydrolysis by Cat-L. Therefore, actin cytoskeleton is destroyed. Furthermore, the structural proteins of podocytes including CD2AP, ZO-1 and

α-actinin-4 would also be affected, and this disfunction may cause cytoskeleton dynamics break, foot processes loss, filtration barrier damage, eventually leading to development of proteinuria.

Treatment of Proteinuria and Outlook

There are three classical kinds of drugs currently available for treatment of proteinuria: corticosteroids, immunosuppressants and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB). With the deepening of studies on podocyte-related diseases, new action mechanisms of these three drugs have been found. Glucocorticoid receptors are found on podocytes and their activation would cause secretion of cytokines, suggesting glucocorticoids can directly act on podocytes to protect them from renal disorder independently of inhibition of the T cells. Immunosuppressants, especially CNIs (CyclosporinA and Tacrolimus), inhibit the hydrolysis of structural proteins by attenuating the Calcineurin-Synaptopodin pathway, stabilizing podocyte function, thus suppressing proteinuria. ACEI/ARBs are widely used to treat proteinuria and improve renal function. Early studies suggested that these drugs reduce blood filtration and control proteinuria by ameliorating the high perfusion and high pressure in glomerulis.

Latest studies indicate that angiotensin II is capable of inducing Calcineurin signal and podocyte injury through upregulation of Ca^{2+}-Calcineurin signaling components, including TRPC6 [14-16]. Therefore, angiotensin inhibitors not only improve blood flow dynamics, but also protect podocyte and reduce proteinuria by molecular regulation. The discovery of these new mechanisms can help us find new drug targets for the treatment of proteinuria. We also observe that TRPCs and some other pathways are widely distributed inside the body. Therefore, we have an urgent need to look for more specific drugs which can treat diseases while minimizing side effects at the same time. More studies are needed to further clarify the pathogenesis and to accumulate theoretical basis for treatment of proteinuria and glomerular diseases.

Grant Support

This study was supported by the Nature Science Foundation of China (No. 81470953).

Financial Disclosures

None.

Conflicts of interest

None.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2019.23.003919

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