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Potential signaling pathway and molecular mechanism of CD2AP associated with proteinuria in glomerular disease

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Abstract

The albuminuria is the early evidence of glomerular filtration membrane damaged and increased permeability. Slit diaphragm is a most important part of selective filtration in the glomerulus. CD2 Associated Protein (CD2AP) is one of slit diaphragm molecules, which is associated with proteinuria. Continuous proteinuria increases the risk of cardiovascular event rate and mortality. Hence, we reviewed the potential signaling pathway and the molecular mechanism of CD2AP associated with proteinuria in glomerular disease.

Introduction

Proteinuria is defined as 24-hour urinary protein quantitation exceeding 150 mg or urinary protein/creatinine > 200mg/g, or urinary protein qualitative test positive. Proteinuria in glomerular disease, such as Focal Segmental Glomerulosclerosis (FSGS), IgA nephropathy, membranous nephropathy, and diabetic nephropathy, is detected by albuminuria/creatinine early, and shows to be closely related to podocyte injury [1]. The fissure between two adjoining podocytes is called a split hole, and the surface is covered with a layer of zipper-like Slit Diaphragm (SD). SD plays a role of size selective filtration in the glomerulus, and decomposition of SD is considered as a common feature of proteinuria [2].

CD2 Associated Protein (CD2AP), a scaffold protein with a molecular weight of 80kD encoded by the CD2AP, is one of SD molecules [3-7]. Some studies showed that CD2AP deficiency was closely related to proteinuria. CD2AP-deficient mice died of renal failure at 6-7 weeks of age [8]. The podocytes of CD2AP Knockout (KO) mice were observed under electron microscope as defects of foot processes and extracellular abnormal material deposition [9]. CD2AP mutation was found in a patient with primary FSGS [10]. Tsuji et al. [11] reported that the endothelial damage, endothelial integrity and disrupted podocyte were detected in CD2AP-KO mice by high-resolution helium ion scanning microscopy.

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Continuous proteinuria can increase the risk of cardiovascular event rates and mortality [12]. For the reason that the significance of CD2AP in the filtration barrier, renal function and relation with proteinuria, we performed this review to summarize potential signaling pathway and molecular mechanism of CD2AP associated with proteinuria in glomerular disease.

Co-expressing molecules

Welsch et al. [13] suggested that CD2AP and p130Cas were colocalized with F-actin in mouse podocytes and possessed different functions, and p130Cas was found in focal adhesions, while CD2AP appeared to be involved in the regulation of F-actin structures in podocyte foot processes. Saito et al [14] showed that neurexin was colocalized with CD2AP at the SD area by dual-labeling analyses, and suggested that neurexin was the component of SD and involved in maintaining its function.

Potential signaling pathways

Transforming Growth Factor-β (TGFβ) can induce cell proliferation, cell differentiation and cellular morphogenesis that contribute to important characteristics of tissue homeostasis [15]. Schiffer et al. [16] performed studies *in vivo* and *in vitro*, and reported that CD2AP was a selective activation in survival and inhibited cell apoptosis signaling pathways mediated by TGFβ1 in mouse podocytes. Furthermore, TGF-β1 could induce podocyte apoptosis and dysfunction of CD2AP, which were the early pathological characteristics of FSGS. Furthermore, Woroniecki et al. [17] conducted an investigation in CD2AP-/- mice and found that, the expression of TGFβ1 was notably increased in CD2AP-/- mice when compared to control normal mice, which indicated that, when the expression CD2AP was inhibited, the TGFβ1 expression was increased and CD2AP-/- mice developed into FSGS.

The Phosphatidylinositol-3-kinase (PI3K) pathway can regulate various target proteins associated with cell proliferation, survival, and cell growth [18]. Huber et al. [19] performed a study in human embryonic kidney cells and mouse podocytes, demonstrated that CD2AP, nephrin and podocin stimulated the PI3K-dependent signaling pathways, and suggested PI3K/AKT worked as an essential signaling pathway to maintain podocytes functional integrity *in vivo*. Xavier et al. [20] detected the signaling pathways in mouse podocytes and transgenic mice, and suggested that, CD2AP was required in the interaction between the TGF-β receptor type I and the P85 subunit of PI3K, and CD2AP/PI3K/AKT pathways mediated directly for the survival of podocyte. Via maintaining the expression of PI3K-AKT-GSK3β, dexamethasone stabilized the expression and subcellular distribution of CD2AP, and it exerted the influence to sustain renal function [21]. Ha et al. [22] suggested that diabetic conditions induced the phenotypical changes of podocyte CD2AP via PI3K/Akt signaling.

CIN85 (a paralog of CD2AP) and CD2AP are the members of the adaptor proteins family, which primarily participate in endocytosis and down regulate activity of receptor tyrosine kinase. In some tissues, CIN85 is likely to make up the loss of CD2AP, like the basal seminiferous tubule [23]. Tossidou et al. [24] investigated that impaired intracellular signaling pathways with subsequent podocyte damage were the reason for the delayed podocyte injury in CD2AP (-/-) mice, and reported that CD2AP/CIN85 balance determined receptor tyrosine kinase signaling response in podocytes. They subsequently found out functional competition for nephrin and podocin between CIN85/RUK (L) and CD2AP [25]. Subsequently, they showed that CIN85 was upregulated in the absence of CD2AP, but was postranslationally modified by SUMOylation in the presence of CD2AP [26].

SV2B is presumed to contain twelve conserved transmembrane domains, and exists in the synaptic vesicles and neuroendocrine granules of vertebrates [27]. Miyauchi et al. [28] found that SV2B was also found in podocyte and may regulated the expression and proper localization of CD2AP. SV2B mRNA decreased before the risk of proteinuria in PAN nephropathy and CD2AP was decreased when small interfering SV2B RNA was used to inhibit the SV2B gene expression. Fukusumi et al. [29] displayed a interaction between SV2B and CD2AP, and the expression of PI3K pathway was not changed in SV2B KO mice.

Yaddanapudi et al. [3] found a possible molecular mechanism that CD2AP regulated the expression of CatL to increase the sensitivity of apoptosis to TGF-β1, and meanwhile CD2AP itself was hydrolyze by CatL. Saurus et al. [30] suggested that inhibition of SHIP2 reduced the expression of CD2AP. Heidet et al. [31] conducted an investigation in nail-patella syndrome kidneys and suggested that heterozygous mutations of LMX1B was not associated with the expression of CD2AP in nail-patella syndrome. Tapia et al. [32] showed that excessive circulating semaphorin3a induced the down regulation of CD2AP, podocin and nephrin in acute proteinuria model.

Fukusumi et al. [33] showed some SD associated molecules in their review, and reported that SV2B, ephrin-B1 and neurexin were conceivable participating in the regulation of the barrier function for nephrotic syndrome. Ha TS. [34] summarized three signal transduction in podocyte biology (Nephrin-Neck-neuronal Wiskott-Aldrich syndrome protein complex, Nephrin-CD2AP-phosphoinositide 3-kinase/Akt complex and P-Cadherin-β-catenin-Wnt signaling), and found they were important in maintaining the normal function of podocyte. Kawachi et al. [35] explored that SV2B and Ephrin-B1 were the functional molecules by regulating the SD function and they were related to the expression of CD2AP. Lemley et al. [36] described that the transcription of several genes in podocytes (e.g. NPHS2, CD2AP) were possibly regulated by LMX1B.

Lu et al. [37] indicated that some siRNAs (Clic3, AOX1 and AIF1L) tended to upregulate the CD2AP expression, and knockdown of genes (MYOM2, CYB5R4, ANXA4, IFT80, GPC1, NSF, ZNF277, MTSS1, ITGAV and CRYAB) would down regulate the expression of CD2AP.

Conclusion

We reviewed the potential signaling pathway and molecular mechanism between CD2AP and proteinuria in glomerular disease. In our review, TGFβ1-CD2AP, CD2AP/PI3K/AKT, and SV2B-CD2AP were abnormal in kidney disease. However, there still need more studies to determine the relationship among them. Furthermore, there seemed to be a link between CD2AP and CIN85. At last, p130Cas and neurexin colocalized with CD2AP in podocyte, which needs more experiments to explore the links between them.

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