COMMENTARY

SRGAP2a: A New Player That Modulates Podocyte Cytoskeleton and Injury in Diabetes

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Podocyte injury and podocyte loss are common features in diabetic kidney disease (DKD). Podocyte detachment and decreased podocyte numbers occur in patients with type 1 or type 2 diabetes and correlate with the progression of renal disease (1–5).

Podocytes play a critical role in the maintenance of the glomerular tuft and the filtration barrier. Foot processes of adjacent podocytes interdigitate to form narrow filtration slits that are bridged by the slit diaphragm (6–9). Podocyte foot processes form the final barrier to protein loss by creating the porous membrane slit diaphragm. Progressive injury and loss of podocytes result in loss of protein in the urine. The resulting microalbuminuria can progress to macroalbuminuria, glomerulosclerosis, and progressive loss of glomerular filtration rate that are hallmarks of DKD (10,11).

The actin cytoskeleton plays an essential role in maintaining podocyte cell structure and interactions with structural molecules in the slit diaphragm. Alterations in the actin cytoskeleton therefore play an important role in podocyte membrane dynamics, podocyte morphology, and podocyte dysfunction (7,12–15).

Monogenic mutations of proteins that regulate podocyte actin dynamics are associated with renal diseases. Examples of these include actinin α 4 (ACTN4) (16), ρ GDP dissociation inhibitor α (ARHGDIA) (17), ρ GTPase-activating protein 24 (ARHGAP24) (18), inverted formin 2 (INF2) (19,20), fat cadherin 1 (FAT1) (21), KN motif and ankyrin repeat domains 2 (KANK2) (22), anillin actin binding protein (ANLN) (23), the actin binding protein ezrin (14), and intraflagellar transport 139 homolog (IFT139) (tetratricopeptide repeat domain 21B [TTC21B]) (24). In addition, slit diaphragm and actin cytoskeleton interactions, including CD2-associated protein (CD2AP) (25), nephrin (NPHS1) (26), and podocin (NPHS2) (27), are associated with renal disease, including nephrotic syndrome and focal segmental glomerulosclerosis (FSGS).

In this issue of *Diabetes*, Pan et al. (28) identified yet another protein that regulates podocyte cytoskeleton dynamics. They analyzed the transcriptional profile of renal biopsy from patients with type 2 DKD and control donors, and among several proteins, they identified SLIT-ROBO ρGTPase-activating protein 2a (SRGAP2a) as one of the main "hub" genes that are strongly associated with proteinuria and glomerular filtration rate in type 2 DKD patients. Immunofluorescence staining and Western blot analysis revealed that human and mouse SRGAP2a primarily localized at podocytes and largely colocalized with synaptopodin. They found that podocyte SRGAP2a is decreased in DKD patients and in *db/db* mice. In addition, SRGAP2a is also decreased in podocytes cultured in the presence of tumor growth factor-β (TGF-β) or high concentration of glucose. In contrast, exogenous SRGAP2a protected the podocytes from the deleterious effects of TGF-β and high concentration of glucose. A critical role for SRGAP2a in podocyte function was also demonstrated in zebrafish, in which knockdown of SRGAP2a, a SRGAP2 ortholog in zebrafish, resulted in podocyte foot process effacement.

SRGAP2a knockdown in podocytes rearranged the podocyte cytoskeleton and increased podocyte motility. Functional and mechanistic studies showed that SRGAP2a suppressed podocyte motility through inactivating RhoA and Cdc42 but not Rac1. RhoA, Cdc42, and Rac1 are small GTPases that have been shown to modulate cytoskeletal dynamics through actin nucleation factors. Furthermore, increasing podocyte SRGAP2a level in *db/db* mice via administration of adenovirus-expressing SRGAP2a significantly decreased podocyte injury and proteinuria (Fig. 1).

These results demonstrate that SRGAP2a protects podocytes via suppressing podocyte migration and further illustrate the importance of the podocyte cytoskeleton in kidney injury and disease. Future studies need to determine if SRGAP2a also plays an important role in podocyte injury and loss associated with FSGS, a common glomerular lesion also encountered in DKD, and if there are practical means of restoring SRGAP2a levels

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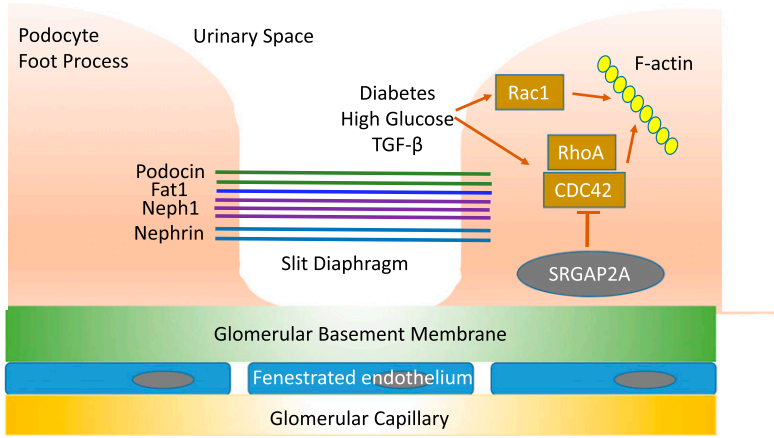

Figure 1—SRGAP2a suppresses podocyte motility through inactivating RhoA/Cdc42.

and function in the podocytes of human subjects with DKD and/or FSGS.

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