Minireview

Store-operated Ca^{2+} channel signaling: Novel mechanism for podocyte injury in kidney disease

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Impact statement

Podocyte integrity is critical for normal glomerular filtration, and podocyte injury is implicated in the pathogenesis of proteinuria in kidney diseases. During the past decade, store-operated Ca^{2+} entry (SOCE)-mediated Ca^{2+} signaling has been demonstrated as a central mechanism for maintaining podocyte integrity, and it is increasingly evident that abnormal store-operated Ca^{2+} channel (SOC) function contributes to podocyte damage. This review integrates recent progress on podocyte physiology and pathophysiology with new insights regarding SOCE-initiated signaling. These advances in our understanding of the mechanisms of physiological podocyte homeostasis and pathological podocyte injury are providing the foundation to develop drugs targeting podocyte SOC to treat kidney diseases.

Abstract

Studies over the last decade have markedly broadened our understanding of store-operated Ca^{2+} channels (SOCs) and their roles in kidney diseases and podocyte dysfunction. Podocytes are terminally differentiated glomerular visceral epithelial cells which are tightly attached to the glomerular capillary basement membrane. Podocytes and their unique foot processes (pedicels) constitute the outer layer of the glomerular filtration membrane and the final barrier preventing filtration of albumin and other plasma proteins. Diabetic nephropathy and other renal diseases are associated with podocyte injury and proteinuria. Recent evidence demonstrates a pivotal role of store-operated Ca^{2+} entry (SOCE) in maintaining structural and functional integrity of podocytes. This article reviews the current knowledge of SOCE and its contributions to podocyte physiology. Recent studies of the contributions of SOC dysfunction to podocyte injury in both cell culture and animal models are discussed, including work in our laboratory. Several downstream signaling pathways mediating SOC function in podocytes also are examined. Understanding the pivotal roles of SOC in podocyte health and disease is essential, as SOCE-activated signaling pathways are potential treatment targets for podocyte injury-related kidney diseases.

Keywords: Ca^{2+} signaling, kidney disease, Orai1, podocyte, proteinuria, STIM1, store-operated Ca^{2+} channel

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Physiology and molecular biology of store-operated Ca^{2+} channels

Store-operated Ca^{2+} channels (SOC), which open when intracellular Ca^{2+} stores are depleted, play central roles in podocyte signaling.[1] Physiologically, G protein coupled receptors and receptor tyrosine kinases activate phospholipase C (PLC) β and γ isoforms, respectively, which in turn hydrolyze phosphatidylinositol 4,5-bisphosphate, yielding diacylglycerol and inositol 1,4,5-trisphosphate (IP_3).[2,3] IP_3 interacts with its (sarco)endoplasmic reticular membrane receptors to elicit Ca^{2+} discharge from (sarco)endoplasmic reticulum.[4,5] Depletion of these Ca^{2+} stores activates SOC in the plasma membrane, allowing extracellular Ca^{2+} to enter the cell.

Initially termed *capacitative* Ca^{2+} entry, store-operated Ca^{2+} entry (SOCE), via SOC was first proposed in 1976 by Putney, who studied the refilling of intracellular Ca^{2+} stores after their depletion by the PLC-linked agonists carbachol and phenylephrine.[6] Subsequent studies combining Ca^{2+} imaging and patch clamp techniques demonstrated that endoplasmic reticular Ca^{2+} depletion in leukemic T cells[4] and mast cells activated Ca^{2+} conductance.[5] More recent research defined the biophysical and pharmacological hallmarks of SOC. Multiple SOC subtypes with distinct biophysical properties, for example, Ca^{2+} selective and nonselective cationic SOC, have been identified,[4,5,7–10] and SOC subtype expression is cell type- and tissue-specific.[4,5,8,9,11] However, a property of all SOCs is the dependence of their activation on depletion of their internal Ca^{2+} stores, not on cytosolic Ca^{2+} concentration.[9,12,13] This unique property distinguishes SOCs from nonselective Ca^{2+}-activated cation channels.

In the decades following discovery of SOCs, intensive research effort encompassing physiology, pharmacology, cell biology and molecular biology has focused upon identifying the molecular components of SOCs and delineating their gating mechanisms. Around the turn of the 21st century, the transient receptor potential canonical (TRPC) channel family

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garnered the most attention,[1,14] and numerous studies identified critical contributions of TRPC channel isoforms to SOC gating.[15–21] However, important differences in the pharmacological and biophysical properties of SOCs *versus* TRPC channels questioned whether TRPC proteins are truly SOC components. Concurrently, the mechanisms activating SOCs were examined. Three major mechanisms were proposed involving (1) diffusible messengers,[22] (2) vesicle fusion/exocytosis,[23] and (3) physical interaction of IP_3 receptors located on ER and Ca^{2+} channels on cell plasma membrane[24] including TRPC channels. Evidence for these mechanisms was equivocal until 2005 to 2006, when stromal interaction molecules (STIM) and Orai proteins were revealed by gene array and high throughput RNA interference screening.[25–29] STIM1 contains a single transmembrane domain, is localized in the endoplasmic reticular (ER) membrane, and functions as a sensor monitoring luminal Ca^{2+} concentration in the ER. When ER Ca^{2+} is depleted, STIM1 aggregates and migrates toward ER-plasma membrane junctions, leading to physical interaction with Orai1, which is the pore-forming unit of SOCs located on the cell plasma membrane, at STIM1: Orai1 stoichiometries ranging from 1:1 to 2:1. This interaction activates Orai1, permitting Ca^{2+} influx from the extracellular fluid into the cytosol.[30–32]

In addition to STIM1 and Orai1, STIM2, a closely-related mammalian STIM1 homolog, and the mammalian Orai1 homologues Orai2 and Orai3 also may constitute and/or regulate SOC, but with distinct functional properties.[33–38] The recent identification of Orai1 α and β splicing variants[39,40] and the STIM1 splicing variant STIM1L,[41–44] which generate SOCs with distinct signaling and regulatory properties, adds another layer of complexity to Orai/STIM-constituted SOCE. Several TRPC isoforms, which initially were proposed as SOC molecular components before Orai1 and STIM1 were discovered, may also function as SOC by interacting with STIM1 and/or Orai1.[45–52] The composition of SOCs is still under investigation.

SOC in podocytes

Podocytes are pivotal determinants of the molecular selectivity of glomerular filtration. Located on the external face of the glomerular basement membrane (GBM), these terminally differentiated, polarized, highly specialized visceral epithelial cells constitute the glomerular filtration barrier's outermost layer (Figure 1).[53–55] Several primary processes extend from the podocyte cell body, from which further extend secondary and even tertiary foot processes, termed pedicels. Those structures encircle the basement membrane surrounding the glomerular capillaries.[54] Spanning the narrow gaps between adjacent foot processes are slit diaphragms composed of highly specialized adhesion molecules including nephrin, Neph1 and other junctional proteins. Slit diaphragms contain pores, 30 to 40 nm wide, which permit free filtration of water, electrolytes and small organic solutes from the glomerular capillaries to the urinary (Bowman's) space, while restricting filtration of albumin and other plasma proteins.[56]

Under physiological conditions, the intact GBM and podocytes maintain essentially protein-free glomerular filtration. However, inflammatory, metabolic or mechanical stimuli associated with various diseases provoke distinctive and substantial changes in podocyte morphology termed foot process simplification and effacement. During this process, cytoskeletal re-arrangements widen and shorten the individual foot processes; in more severe cases, the secondary and tertiary processes are resorbed into the primary processes.[54,57–59] Foot process effacement and simplification exposes the outer face of the GBM, increasing the protein permeability of the glomerular filtration barrier and producing pathological proteinuria.

As in vascular smooth muscle and glomerular mesangial cells, the structural integrity of podocytes depends on the maintenance of Ca^{2+} homeostasis inside the cell. In podocytes, multiple signaling mechanisms controlling intracellular Ca^{2+} concentrations converge on plasma membrane ion channels. Podocyte Ca^{2+} signaling has been studied most extensively in TRPC5 and especially TRPC6 channels.[60–65] Recently, SOCE and the SOC components Orai1 and STIM1 have been reported in podocytes.[66,67]

In 2013, podocyte SOCE was first reported by Yang *et al.*,[66] who studied signaling mechanisms activating podocyte apoptosis in response to high glucose concentrations. Using Ca^{2+} imaging, they showed that thapsigargin, a (sarco) endoplasmic reticular ATPase inhibitor which depletes ER Ca^{2+} stores, activated SOCE in cultured podocytes. Recent electrophysiology evidence from our group also supports existence of SOC in podocytes. By use of whole cell patch clamp, we recorded thapsigargin-stimulated inward currents in cultured human podocytes which were blocked by La^{3+}, an inhibitor of SOCE.[67] Acting on its AT1 receptors, angiotensin II, an important regulator of podocyte physiology and pathology,[63,64] activates the PLC-IP_3 signaling pathway, which could open SOCs via IP_3-induced ER Ca^{2+} release. Indeed, we demonstrated in human podocytes that angiotensin II evoked robust inward Ca^{2+} currents which were suppressed by the SOC blocker 3,5-bis(trifluoromethyl) pyrazole 2.[67]

Expression of the channel or channel-gating proteins in cultured mouse and human podocytes further demonstrated the fundamental role of SOCE. In 2015, Xu *et al.*[68] reported that the saturated fatty acid palmitate induced STIM1 oligomerization, the initial step in SOC activation, in ER membranes of cultured mouse podocytes, possibly through PLC signaling. As expected, palmitate elicited SOCE,[68] although the functional consequences of palmitate-stimulated SOCE were not evaluated.[68]

Although mounting biochemical, biological and functional evidence unambiguously supports existence of SOC in podocytes, this evidence was obtained almost exclusively in cultured cells, and *in vivo* data are lacking. Future studies should be directed toward confirming podocyte SOC in intact animals. Furthermore, to date all biochemical and molecular studies of SOC in podocytes have focused on Orai1 and STIM1, the prototypical SOC channel and gating proteins, respectively. However, homologs (Orai2, Orai3, and STIM2)[33–38] and splicing variants (Orai1α, Orai1β, and STIM1L)[39–44] of the two proteins have not been studied in podocytes. These homologs and splicing variants reportedly function as SOC or gate/regulate SOC in other cell types.[33–44] Moreover, the location of SOC in podocytes should be

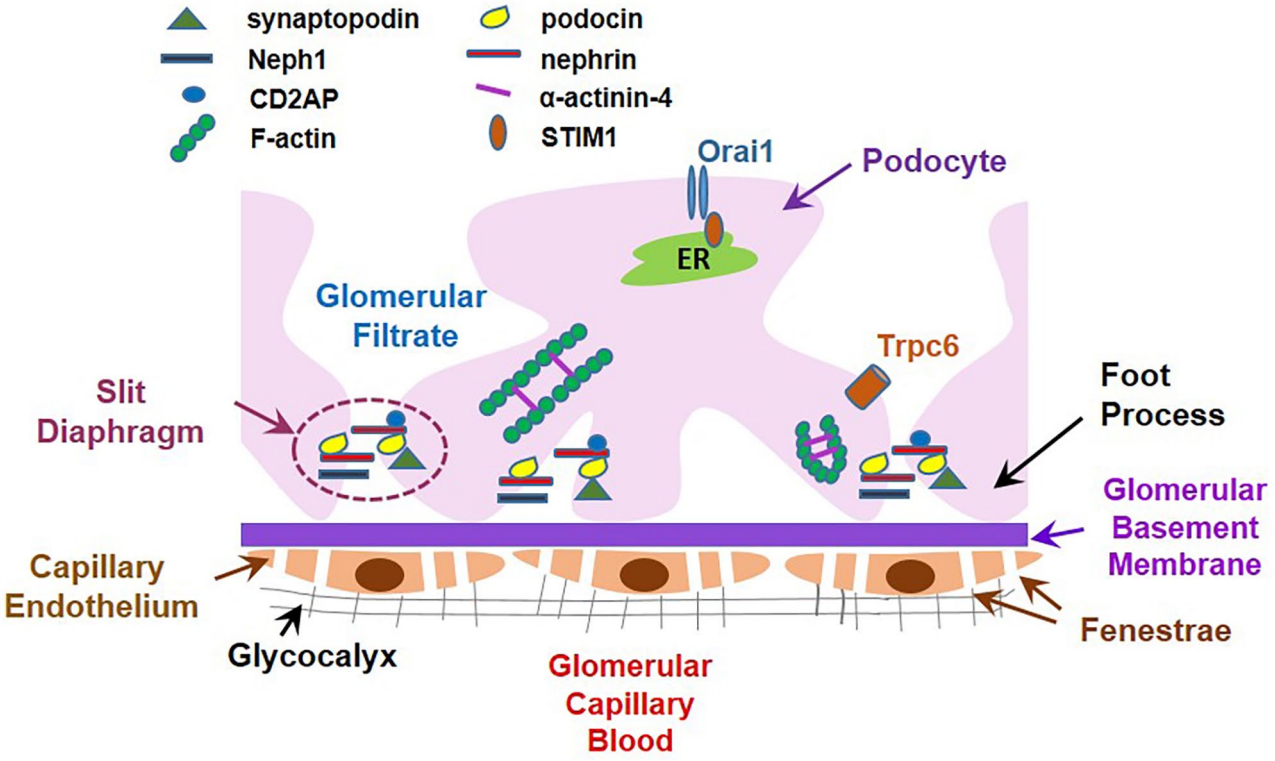

Figure 1. Podocyte structure and connections with glomerular basement membrane.
CD2AP: CD2-associated protein; ER: endoplasmic reticulum; GBM: glomerular basement membrane; Neph1: nephrin 1; SD: slit diaphragm; STIM1: stromal interaction molecule 1; TRPC6: transient receptor potential.

identified, because the downstream pathways and functions of SOC in foot processes may differ from those in the cell body. For instance, TRPC6 activation in the podocyte cell body modulates gene expression,[69] but in foot process alters slit diaphragm permeability.[70,71]

It should be noted that various SOC subtypes may exist with cell type–specific distributions and distinct biophysical and pharmacological profiles.[1] Although formation of highly Ca^{2+}-selective SOC by homo- or heteromultimeric Orai subunits is widely accepted, nonselective SOCs may also be formed by Orai-TRPC channel interactions.[40,72] Indeed, Orai1-TRRPC1 interactions were indispensable for functional SOCE activation in human embryonic kidney (HEK293) cells[45] and osteoclasts.[48] Although podocytes possess Orai1 and TRPCs 5 and 6, whether these proteins act independently or cooperatively is unclear and awaits more molecular, biophysical, and pharmacological evidence.

Physiological impact of podocyte SOCs

Podocytes integrate with the glomerular endothelial cells to build and maintain the GBM. Collectively, podocytes, GBM, and the glomerular endothelium with its surface glycocalyx constitute the interface that effects glomerular filtration. The slit diaphragms bridging the adjacent podocyte foot processes impose steric hindrance selectively limiting filtration of protein-size molecules. As in many cell types, podocyte structure and function are largely regulated by intracellular Ca^{2+} signals and podocyte Ca^{2+} homeostasis is, to a large extent, attributed to plasma membrane Ca^{2+} channels. Emerging evidence suggests that SOC and its downstream signaling help maintain podocyte integrity and, thus, normal glomerular filtration.

Miao *et al.*[73] found that STIM1 and Orai1 overexpression lowered contents of the slit diaphragm proteins podocin and CD2-associated protein (CD2AP) while increasing content of the cytoskeletal protein α-actinin-4. All these proteins are essential for podocyte integrity and normal structure of the glomerular filtration barrier (Figure 1). As expected, overexpression of STIM1 and Orai1 increased podocyte permeability.[73] Although they did not assess the impact of podocin, CD2AP and α-actinin overexpression on SOC function, Miao *et al*. reported direct evidence that SOC signaling proteins are associated with podocyte structure and function. Recently, in cultured human podocytes we also found that SOCE regulates abundance of the slit diaphragm protein nephrin.[67]

Foot process morphology and podocyte function highly depend on the actin cytoskeleton. Regardless of the initial insult, the ultimate pathway for podocyte damage is actin cytoskeleton rearrangement and dysfunction.[56] Recently, both Kim *et al.*[74] and our group[67] demonstrated in cultured podocytes that Orai1-mediated SOCE contributed to normal distribution and organization of cytoskeleton proteins. Enhancement of the Ca^{2+} signaling resulted in disorganization of cytoskeleton and actin remodeling, an indication of podocyte injury.[67,74]

Pathophysiological relevance of SOC in podocytes

Podocytes are terminally differentiated epithelial cells. Their limited regenerative capacity and their vulnerability to

various diseases make podocyte injury particularly important in glomerular pathology. Loss of sufficient numbers of podocytes inevitably leads to glomerulosclerosis and eventual loss of the nephron. Podocyte structural and functional integrity depend on intracellular Ca^{2+} homeostasis; thus, disruption of intracellular Ca^{2+} signaling contributes to podocyte injury and glomerular disease. In addition to the well-described cause–effect relationship between TRPC6 overactivation in podocytes and focal segmental glomerulosclerosis/proteinuria,[61–64,75] recent evidence indicates that abnormal SOC Ca^{2+} signaling also contributes to podocyte-associated glomerular disease. Miao *et al*.[73] demonstrated elevated abundances of mRNA encoding STIM1 and Orai1 in renal cortex of mice with adriamycin-induced nephropathy *versus* control mice. STIM1 and Orai1 overexpression decreased contents of slit diaphragm proteins podocin and CD2AP, leading to increased permeability of mouse podocytes.[73]

The leading cause of chronic kidney disease in the United States, diabetic nephropathy (DN) is characterized by microalbuminuria in its early stages which intensifies into fulminant proteinuria as the disease progresses. Also in the early stages of DN, glomerular hyperfiltration imposes shear stress which damages podocytes.[76] Podocyte injury and loss disrupts the glomerular filtration barrier, allowing plasma proteins to pass from the glomerular capillaries into Bowman's space. Excessive protein in the proximal tubular lumen overwhelms tubular capacity for endocytosis, allowing albumin and other plasma proteins to spill into the urine. The contributions of abnormal SOC signaling to podocyte pathology in DN are the focus of ongoing, intensive research. Jin *et al*.[77] found that both STIM1 and STIM2 contents increased in kidneys of rats and patients with diabetic kidney disease. STIM1 and Orai1 overexpression increased Ca^{2+} influx in cultured mouse podocytes, and increased Ca^{2+} entry provoked podocyte epithelial-to-mesenchymal transition (EMT) in humans and rats with DN.[77,78] Furthermore, increased podocyte STIM1 content augmented Orai1-mediated Ca^{2+} entry in rats with diabetic kidney disease.[78] Moreover, deletion of STIM1 in cultured podocytes not only ameliorated high glucose-induced podocyte apoptosis and EMT, but also enhanced podocyte autophagy.[77,78] Thus, disordered SOC contributes to podocyte injury in DN.

Podocytes are among several insulin signaling targets in kidney.[79] Insulin receptor signaling is pivotal for podocyte function, and perturbation of podocyte insulin signaling compromises the glomerular filtration barrier, causing proteinuria.[80–82] Recently, Kim *et al*.[74] reported increased podocyte Orai1 plasma membrane trafficking through a Vesicle Associated Membrane Protein 2 (VAMP2)-dependent mechanism in response to insulin stimulation, resulting in enhanced SOCE. Insulin-activated SOCE in podocytes triggered actin remodeling and transepithelial albumin leakage. Intensification of SOCE-induced podocyte injury by insulin signaling was further validated in animals. Genetic *orai*1 overexpression in mice results in podocyte foot processes effacement, compromising the glomerular filtration barrier. In contrast, podocyte-specific Orai1 ablation blunts insulin-stimulated SOCE, synaptopodin depletion, and proteinuria. In diabetic mice, Kim *et al*.[74] showed that podocyte damage and proteinuria coincided with increased Orai1 expression at the hyperinsulinemic stage, and that suppression of Orai1 Ca^{2+} signaling ameliorated the detrimental effects of elevated insulin.

Recently, we demonstrated in cultured podocytes that exposure to elevated glucose concentration-dependently increased Orai1 protein content and SOCE. Furthermore, high glucose provoked overt F-actin remodeling and lowered nephrin content, indicating podocyte injury (Figure 2). Importantly, both pharmacological Orai1 inhibition by BTP2 or genetic *orai1* ablation via CRISPR-Cas9 lentivirus prevent these indicators of podocyte injury (Figure 2). Since hyperglycemia is the main pathogenic factor promoting podocyte injury in DN,[83] these results strongly suggest enhanced SOCE in podocytes is a pivotal contributor to DN pathogenesis.

SOC-initiated signaling in podocytes

Store-operated Ca^{2+} channels are essential to myriad cellular processes including exocytosis, enzyme regulation, gene transcription, proliferation, and apoptosis.[1] Not surprisingly, multiple downstream pathways mediate SOCE-induced physiological and pathological consequences. The diverse SOC signaling pathways could be cell-type specific and cell function dependent. In podocytes, studies on SOC signaling have focused on the intracellular pathways regulating cell phenotype transition, turnover and structural integrity.

Inflammation and immune mechanisms contribute to DN pathogenesis.[84–87] Receptors for the Fc domains of immunoglobulin G antibodies (FcγRs) trigger phagocytosis, antibody-dependent cellular cytotoxicity, release of inflammatory mediators, and other effector functions.[88] Preventing FcγR activation alleviated renal hypertrophy, inflammation and fibrosis in diabetic mice, suggesting that targeting FcγR may prove renoprotective against DN.[89] Podocyte SOCE signaling is augmented in DN, and increased Ca^{2+} signaling induced podocyte EMT in diabetic kidney,[77,78] a phenomenon associated with renal fibrosis.[90] Jin *et al*.[77,78] demonstrated that FcγRII activation mediated SOCE-activated podocyte EMT, and inhibition of SOCE by STIM1 silencing blunted high glucose-induced FcγRII activity and podocyte injury.[77] Accordingly, targeting the SOCE-FcγRII signaling pathway might be a powerful strategy to treat inflammatory kidney diseases, including DN.

Activation of calcineurin, a serine/threonine phosphatase, requires increased intracellular Ca^{2+} concentrations. In cardiomyocytes and vascular endothelial cells, SOCE-activated calcineurin signaling mediated SOCE-induced hypertrophy[91,92] and apoptosis.[93] Moreover, calcineurin-nuclear factor of activated T cells (NFAT) mediated downstream signaling in podocytes initiated by NMDA receptor- and TRPC6-mediated Ca^{2+} entry.[70,71,94,95] Recently, Kim *et al*.[74] reported that calcineurin is also a downstream SOCE effector in podocytes. In cultured podocytes and in diabetic mice, calcineurin activation contributed to podocyte injury and proteinuria induced by insulin-activated SOCE. Thus, the insulin-SOCE-calcineurin signaling cascade in podocytes may be pivotal to the pathogenesis of renal disease.

Calpains, a family of Ca^{2+}-activated cysteine proteases highly responsive to increased intracellular Ca^{2+}, also mediate

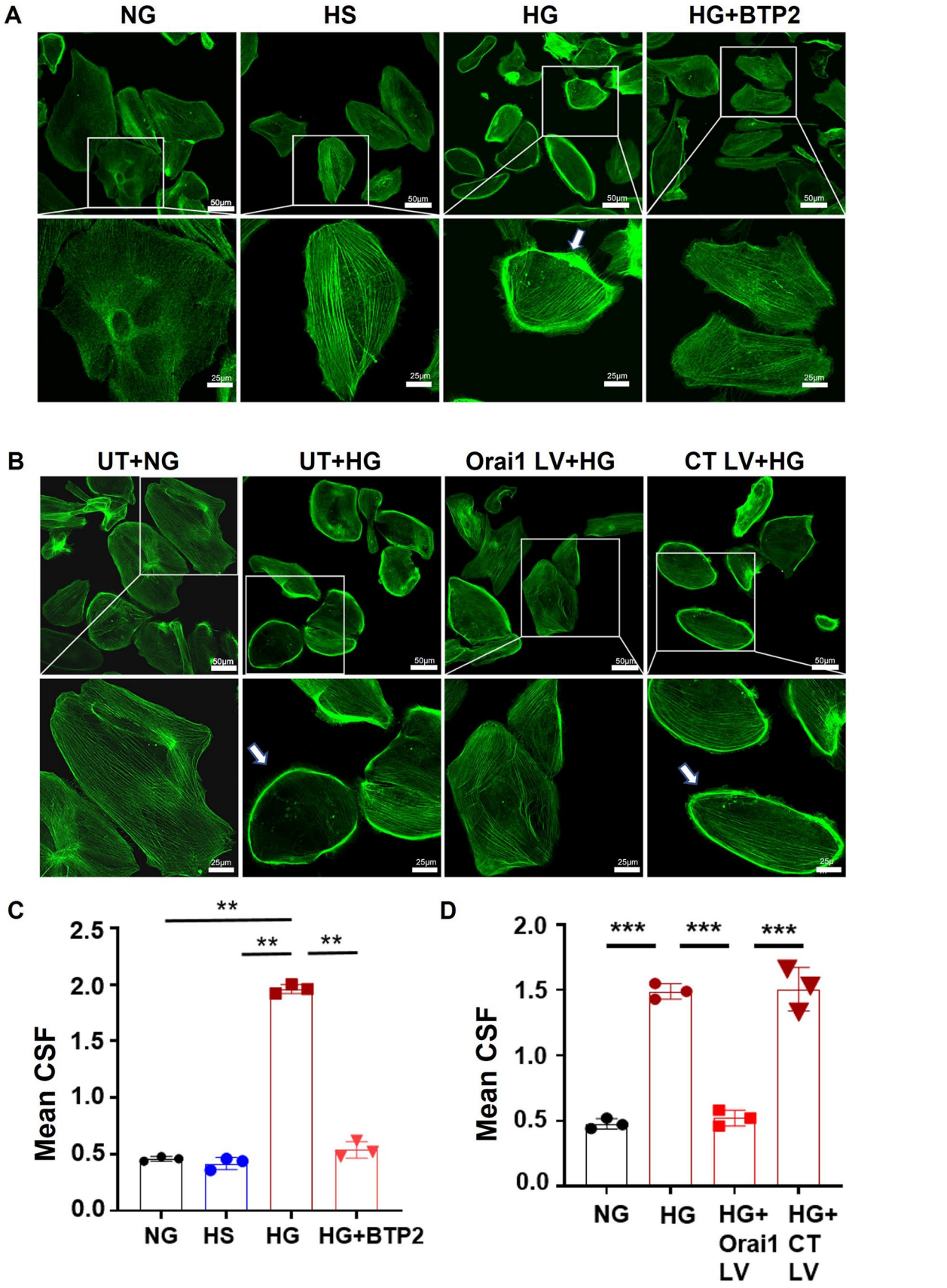

Figure 2. Confocal microscopic images, showing contribution of SOCE to podocyte cytoskeleton organization. (A & B): Representative immunofluorescence staining of F-actin of podocytes with different treatments. (C & D): Statistical analysis of data from experiments presented in A and B, respectively (Adapted from Tao *et al*.[67] with permission of the American Society for Biochemistry and Molecular Biology).

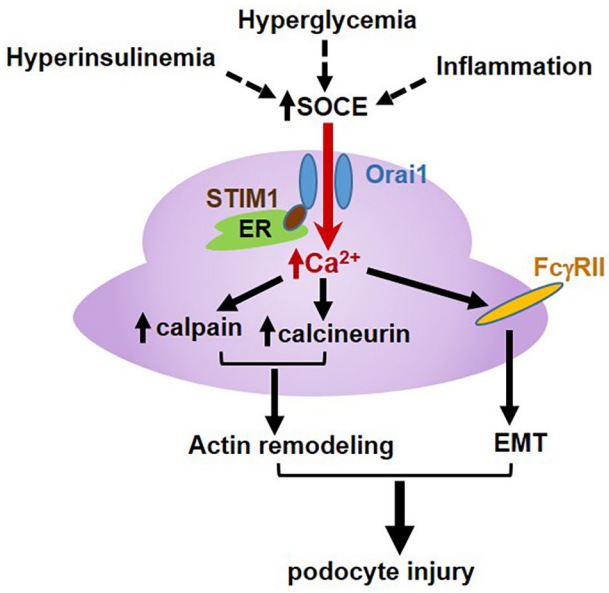

Figure 3. SOCE-initiated signaling pathways in podocytes. In diabetic nephropathy and many other kidney diseases, the activities of one or more of these pathways are upregulated and the increased signaling results in podocyte injury. Broken arrows: putative triggers of the signaling pathways.
EMT: epithelial–mesenchymal transition; ER: endoplasmic reticulum; SOCE: store-operated Ca^{2+} entry; STIM1: stromal interaction molecule 1.

SOCE-initiated signaling in podocytes.[96–98] Activation of TRPC6 in podocytes led to calpain activation.[97,98] Interestingly, Farmer *et al.*[97] demonstrated that calpain is activated by its direct interaction with TRPC6, rather than TRPC6-mediated Ca^{2+} influx. Recently, we demonstrated calpain activation by SOCE-mediated, high glucose-induced injury in cultured human podocytes.[67] Since pharmacological SOC inhibition decreased and SOC activation increased calpain activity,[67] the calpain activation in our study could be ascribed to Ca^{2+} influx through SOCs.

Collectively, multiple pathways have been shown to mediate SOCE signaling in podocytes (Figure 3). These diverse signaling pathways are concordant with the multiple functions of SOC, all of which are critical for podocyte homeostasis.

Concluding remarks

This review has summarized the functions and downstream signaling of SOC in podocytes and its physiological and pathological impact. The evidence reviewed herein demonstrates unequivocally that SOCE is essential to podocyte integrity. As in other cell types, multiple mechanisms regulate SOC function in podocytes, and diverse intracellular messengers mediate SOC Ca^{2+} signaling. Intriguingly, the most substantial evidence relates to the contributions of SOC to cellular processes associated with disease states, for example, ultrastructural changes effecting podocyte simplification and effacement. Therefore, SOC signaling pathways are promising therapeutic targets for podocyte-associated renal diseases. However, several factors must be considered when pursuing such strategies. First, SOCs are ubiquitously expressed in the body, both in excitable and non-excitable cells.[1] Systemic application of SOC modulators in humans will have broad effects, including potential "off-target" consequences within and beyond the diseased organ or system. Second, SOC function is cell type specific. For instance, activation of SOC in glomerular mesangial cells inhibits extracellular matrix production, which is beneficial in diabetic kidney,[99–101] but in proximal tubular cells, SOC activation exacerbates renal fibrosis.[102] Moreover, some evidence in the same cell types from different laboratories seem contradictory. For instance, Soni and Adebiyi[103] reported that SOC stimulated mesangial cell proliferation and synthesis of extracellular matrix proteins; in contrast, SOC inhibited these phenomena in our studies.[99–101] Similarly, Zeng *et al.*[104] demonstrated that SOC inhibition exacerbates proteinuria in DN mice by impairing proximal tubular endocytosis of albumin, a finding divergent from the adverse effects of SOC on proximal tubular cells reported by Mai *et al.*[102] Finally, although many SOC inhibitors have been used over the past 30 years, none has proven to be purely SOC selective.[105] Therefore, podocyte-specific SOC signaling and its regulatory mechanisms must be delineated further to permit interrogation of strategies targeting SOC pathways for treatment of podocyte-related kidney diseases. Indeed, developing targeted delivery of selective agents to podocytes to modulate SOC holds particular promise for addressing SOC-mediated podocyte injury.

AUTHORS' CONTRIBUTIONS

YT drafted, and RTM, KWM, and RM revised and edited the manuscript.

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