MINIREVIEW

Store-Operated Ca^{2+} Channel in Renal Microcirculation and Glomeruli

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Store-operated Ca^{2+} channel (SOC) is defined as a channel that opens in response to depletion of the internal Ca^{2+} stores. During the last decade, many investigators have made a great effort to identify and characterize SOC, and to evaluate its physiologic function and pathophysiologic relevance in a variety of cell lines, primary cultures, and native tissues. To date, accumulating evidence has demonstrated that SOC is an essential Ca^{2+} entry mechanism in vascular smooth-muscle cells of renal microvasculature and glomerular mesangial cells, both of which tightly control glomerular hemodynamics and filtration. Store-operated Ca^{2+}, combined with other types of Ca^{2+} entry channels, constitutes a profile of Ca^{2+} changes in response to physiologic vasoconstrictors and, thereby, regulates renal microcirculation and mesangial function. In addition, SOC is associated with altered Ca^{2+} signaling occurring in diseased kidneys, such as diabetic nephropathy. Although the gating mechanism and molecular identity of SOC are still enigmatic and may be cell-type and tissue specific, data from several independent groups suggest that protein kinase C plays an important role in SOC activation and that certain isoforms of canonical transient receptor potential (TRPC) proteins are candidates of SOC in renal microvessels and mesangial cells.
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Introduction

In eukaryotic cells, both activation of phospholipase (PL)-C β-isozymes by G-protein–coupled receptors and of PLC γ-isoforms by receptor tyrosine kinases result in the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG; Refs. 1, 2). IP_3 evokes an increase in the intracellular Ca^{2+} concentration that is usually composed of two phases, an initial Ca^{2+} transient caused by the release of Ca^{2+} from IP_3-sensitive intracellular stores and an influx of Ca^{2+} from the extracellular compartment. Several channels mediate the Ca^{2+} entry across the plasma membrane. In excitable cells, such as vascular smooth-muscle cells, in addition to the well-known voltage-operated Ca^{2+} channel (VOCC), two other mechanisms, store-operated Ca^{2+} channel (SOC) and receptor-operated Ca^{2+} channel (ROC), have been extensively investigated recently. SOC is activated when IP_3 discharges Ca^{2+} from intracellular stores in the endoplasmic reticulum (ER) or sarcoplasmic reticulum (SR; Refs. 3, 4). During the past 10 years, identification and characterization of SOC and evaluation of its function have become a hot topic in the fields of physiology, pharmacology, cell biology, and molecular biology. The outcome from those studies has been the acknowledgment that SOC is an essential Ca^{2+} entry mechanism in a variety of cell types. In vascular smooth muscle, SOC not only contributes to basic tone, but participates in hormone-induced contraction as well (5–8). This review focuses on SOC in the renal microcirculation and in glomeruli by summarizing the recent findings and development of this novel channel in the specific parts of the kidney. The physiologic and pathophysiologic relevance of the channel are also discussed.

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SOC, a Ca^{2+} Entry Mechanism in Renal Microvasculature

SOC is defined as a channel that opens in response to depletion of internal Ca^{2+} stores. The Ca^{2+} entry *via* SOCs, termed the capacitative Ca^{2+} entry (CCE), was first proposed by Putney on the basis of experiments examining the kinetics of refilling of intracellular Ca^{2+} stores after their depletion by a PLC-linked agonist (9). An important step in this field was the demonstration of a Ca^{2+} conductance activated by store depletion. This current was originally discovered in mast cells and T lymphocytes by means of a combination of Ca^{2+} imaging and patch clamp techniques (3, 4). Intensive studies in the last decade have provided ample information on the biophysical and pharmacologic features of SOC and its function. In terms of biophysical properties, SOC might have multiple subtypes. For instance, both Ca^{2+} selective and nonselective cationic SOC channels have been discovered (3, 4, 6, 8, 10, 11). Expression of SOC subtypes is cell-type or tissue dependent (3, 4, 6, 8, 12). However, a notable characteristic of all SOCs is that SOC activation is not dependent on intracellular Ca^{2+} concentration, but on a reduction of Ca^{2+} within the internal Ca^{2+} stores (6, 13, 14). This unique property is important in distinguishing SOC from Ca^{2+}-activated nonselective cation channels.

SOC-mediated Ca^{2+} entry is a widespread Ca^{2+} influx pathway and is important for regulating a host of temporally diverse processes, from exocytosis to cell proliferation (15). In vascular smooth-muscle cells, evidence has been accumulating to suggest that CCE plays an important role in determining the contractile state at rest and in response to agonist stimulation (5–8). The majority of these studies were conducted in the pulmonary artery, the aorta, and the portal vein. Recently, the existence and function of SOC in the renal microvasculature have been identified by several research groups (16–21). The microcirculation of the kidney is regionally specialized. In the cortex, afferent and efferent arterioles govern the driving forces that promote glomerular filtration. A dense peritubular capillary plexus arising from efferent arterioles surrounds the proximal and distal convoluted tubules to accommodate the enormous reabsorption of glomerular filtrate. The regulatory mechanism for the arteriolar tone has been extensively investigated because the afferent and efferent arterioles are major resistance vessels in the kidney and their contractile state plays a pivotal role in regional blood distribution and in renal function. An earlier study by Carmines *et al.* (16), using fura-2 as an indicator of cytosolic Ca^{2+} concentration, found that the mechanisms of depolarization-induced Ca^{2+} influx were different in afferent and efferent arterioles. Nifedipine abolished the Ca^{2+} response in the afferent arteriole, but not in the efferent arteriole, suggesting that, in the afferent arteriole, the depolarization-induced Ca^{2+} entry was mediated by VOCC and, in the efferent arteriole, another channel mechanism was involved. This segmental heterogeneity in the renal microvasculature in terms of channel mechanism was confirmed by Nagahama *et al.* in the isolated perfused hydronephrotic rat kidney (17), and was further extended by another group who proposed that the channel mediating Ca^{2+} entry in the efferent arteriole was SOC (18). In the isolated rat efferent arteriole, angiotensin (Ang) II evoked a sustained increase in intracellular Ca^{2+} concentration that was blocked by SKF96365, a nonselective cation channel inhibitor, but not by nifedipine. Furthermore, depletion of internal Ca^{2+} stores with a specific SR Ca^{2+} ATPase inhibitor, cyclopiazonic acid, induced an identical rise of intracellular Ca^{2+} to that induced by Ang II in the efferent arteriole. The suggestion that SOCs are predominantly involved in efferent arteriole constriction is challenged by findings from Fellner and Arendshorst (19). In the freshly isolated vascular smooth-muscle cells derived from rat preglomerular vessels, this group found that nifedipine or verapamil only partially inhibited vasopressin-induced Ca^{2+} entry. In the presence of the VOCC blockers, depletion of internal Ca^{2+} stores with cyclopiazonic acid or thapsigargin significantly raised the intracellular concentration in response to Ca^{2+} readmission. These results suggest that SOC also is present and operative in preglomerular vessels. The distinct conclusion from those studies might be explained by discrepancies in the protocols for isolating the microvessels, in the vasoconstrictors used, and in the components or the concentrations of the buffers used in preparing the vessels. Other factors might also contribute to the differential findings, such as differences in the segments of the preglomerular vessels, the diameter of the vessels, and variability of cell types within different arteriolar segments in the same bed, as has been proposed by Archer in the pulmonary vasculature as it relates to K^+ channels (22).

Juxtaglomerular (JG) cells of the kidneys are modified smooth-muscle cells located in the walls of the afferent arterioles immediately proximal to the glomeruli. The major function of the JG cells is to synthesize, store, and release renin into the blood flow for initiating the renin-angiotensin-aldosterone system. Ca^{2+} plays an unusual role in the control of renin secretion from the renal JG cells in that an increase in the Ca^{2+} concentration inhibits the exocytosis of renin. In isolated perfused rat kidney, store-operated Ca^{2+} influx has been shown to negatively regulate renin secretion by JG cells, suggesting that SOC might be an important mechanism in control of blood volume and blood pressure (20).

Most recently, CCE was also discovered in renal cortical interlobular arteries because cyclopiazonic acid and thapsigargin stimulated a robust Ca^{2+} influx measured by fura-2 ratiometric fluorescence. These responses were dose-dependently blocked by Gd^{3+} and 2-aminoethoxydiphenyl borate (2-APB; Ref. 21), both of which are relatively selective to SOC at low concentrations (23–25).

Unlike VOCC, the activation mechanism of SOC is far from clear. Three major hypotheses have been proposed and

none is accepted unanimously. It is possible that the activation mechanism of SOC is cell-type or tissue specific. Readers are directed to a recent comprehensive review for details (15). In renal microvasculature, protein kinase C (PKC) might be a critical mediator between store depletion and SOC opening. This inference is based on the studies that Ang II–stimulated Ca^{2+} influx in the efferent arteriole was mediated by SOC (18) and Ang II–induced constriction of the efferent arteriole was abolished by a PKC inhibitor (17). In addition, activation of PKC could mimic the Ang II–induced response in the efferent arteriole (17). Interestingly, the PKC-involved mechanism of SOC activation was also observed in rabbit portal vein myocytes (7). In addition to PKC, another molecule, termed Ca^{2+} influx factor (CIF), should be taken into account for controlling SOC activity. The CIF, derived from partially purified extracts from a genetically store-depleted yeast (*pmr 1* yeast), was originally shown to activate Ca^{2+} influx in Xenopus oocytes and Ca^{2+} release-activated Ca^{2+} current (I_{CRAC}, a typical SOC current) in Jurkat cells (26), and later on was found to directly activate an endogenous SOC in vascular smooth-muscle cells (27). A CIF-like endogenous factor produced by human platelets with depleted Ca^{2+} stores was also shown to activate native SOC in isolated inside-out membrane patches excised from vascular smooth-muscle cells (27). A further study from the same group proposed that the CIF-induced SOC activation in vascular smooth-muscle cells might be through plasma-membrane–delimited events in which calmodulin, Ca^{2+}-independent PLA_2, and lysophospholipids were involved (28). However, a major concern regarding this hypothesis is the nature of CIF. Is it a pure molecule or a composite substance? Figure 1 depicts

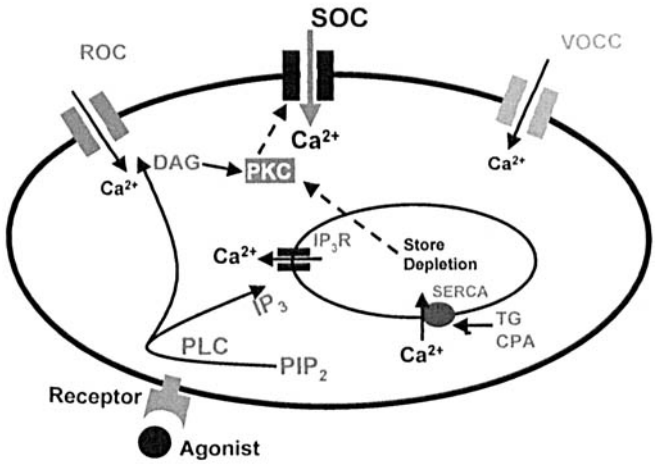

Figure 1. Major Ca^{2+} entry pathways in renal arteriolar smooth-muscle cells and glomerular MCs. A vasoconstrictor binds to its G-protein–coupled receptor and activates PLC, which converts PIP_2 into IP_3 and DAG. IP_3 releases Ca^{2+} from the SR *via* the IP_3 receptor. Released Ca^{2+}, store depletion, and DAG activate VOCC, SOC, and ROC, respectively, through distinct mechanisms. In addition, selective inhibitors of SR/ER Ca^{2+} ATPase (SERCA), thapsigargin (TG), and cyclopiazonic acid (CPA), also deplete internal Ca^{2+} stores and open SOC. PKC is involved in SOC activation.

major Ca^{2+} influx pathways currently discovered in renal microvascular smooth-muscle cells in response to vasoconstrictors, with emphasis on store-operated Ca^{2+} entry and its possible intracellular signaling pathway.

SOC, a Physiologic Player in Regulating Function of Glomerular Cells

Several types of cells reside in glomeruli, including mesangial cells (MCs), podocytes, endothelial cells, and visceral epithelial cells. In the glomerulus, MCs have many beneficial roles, which include production of growth factors that allow normal cell turnover, production of mesangial matrix to provide structural support for glomerular capillaries, and modulation of glomerular hemodynamics through their contractile properties. MCs demonstrate vasopressor hormone signaling and contractile responsiveness, similar to renal arteriolar smooth-muscle cells. Because MCs are readily cultured from isolated glomeruli, maintaining Ang II, vasopressin, and endothelin-1 signaling and contractile function throughout many passages (29, 30), mesangial function and intracellular signaling pathways have been extensively studied at cellular and molecular levels (31–35). During the last 10 years, we and others have made a great effort to explore the function and regulatory mechanism of SOC in MCs.

The first evidence for CCE in MCs was provided by Menè using fura-2 fluorescence techniques (36). In that study, emptying of ER by Ang II, thapsigargin, or ionomycin significantly potentiated Ca^{2+} influx in response to Ca^{2+} readmission to the extracellular compartment in cultured human MCs. The enhanced response was not affected by cell membrane depolarization, suggesting that VOCC was not responsible for such potentiation. This finding was further confirmed by other groups, including ours, in cultured rat and human MCs (12, 31, 32, 35, 37). Direct evidence for SOC in MCs comes from patch-clamp experiments conducted by Ma *et al.* (12). In cell-attached patches, we were able to detect single-channel currents in response to thapsigargin in cultured human MCs preincubated with 1,2-bis (aminophenoxy) ethane-N,N,N′,N′-tetra-acetic acid (BAPTA)/acetoxymethyl ester (AM; Fig. 2 A). These currents were characterized with a very low single-channel conductance (2.1 pS with Ba^{2+} as charge carriers), high Ca^{2+} selectivity (87/8.2/1 for $Ca^{2+}/Ba^{2+}/K^+$), positive reversal potential (63 mV, 90 m*M* Ba^{2+} in the pipet solution; Fig. 2B), and blockade by low concentration of La^{3+} (2 μ*M*). All of these properties are consistent with those of SOC described in other cell types (3, 13, 38). In addition, the open probability of the channel was independent of membrane potential, confirming that the channels observed were not VOCC. The SOC in MCs was further confirmed in whole-cell patch-clamp recordings in which the whole-cell currents in response to thapsigargin or Ang II exhibited inward rectification, a hallmark of SOC (33). Apparently, SOC constitutes a Ca^{2+} entry mechanism in MCs.

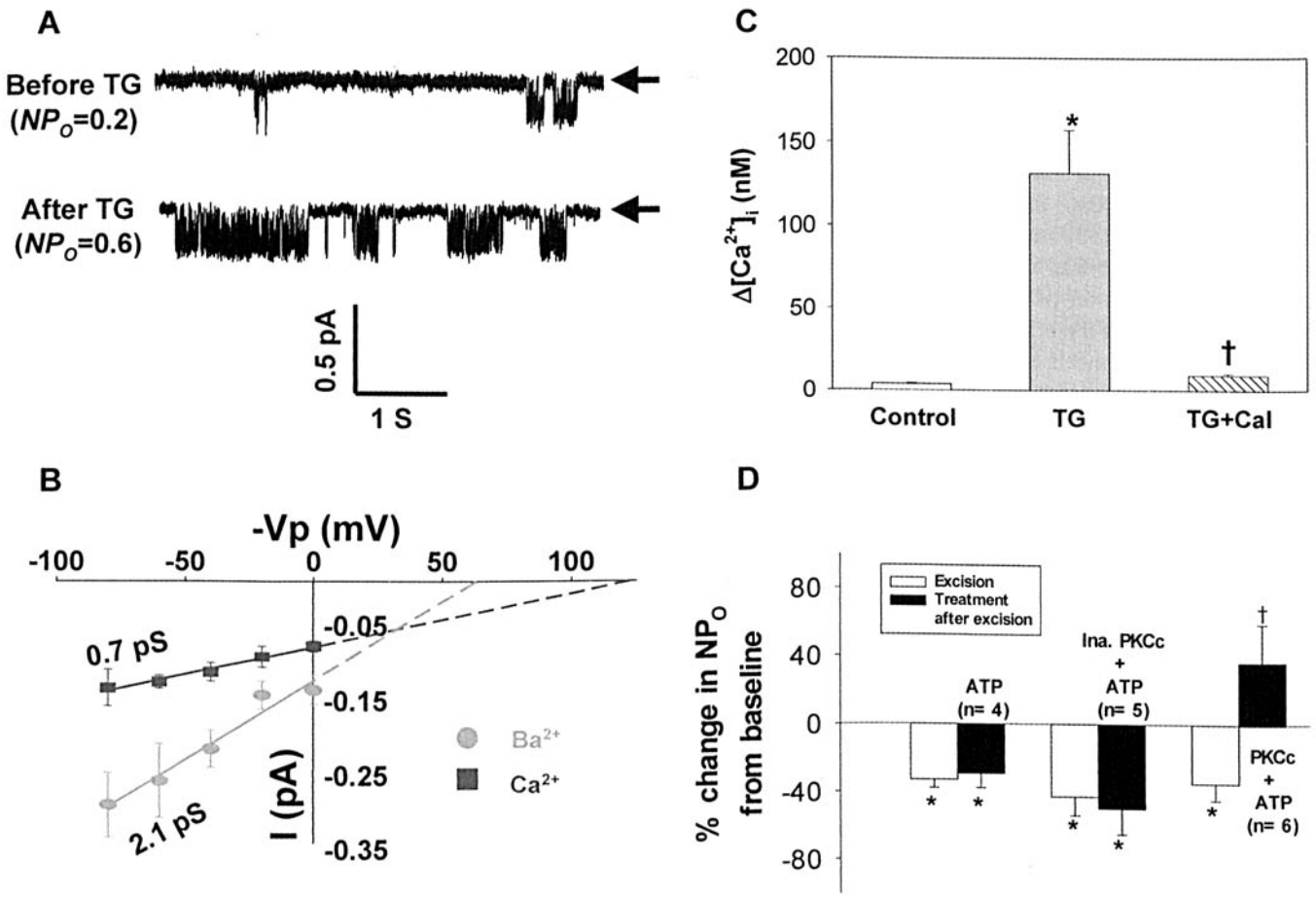

Figure 2. Patch clamp and fura-2 fluorescence ratiometry experiments showing SOC in MCs and the contribution of PKC to SOC activation. (A) Representative traces of single-channel currents in response to TG. MCs were preincubated with 10 μM BAPTA/AM for 30 mins. The holding potential was 80 mV (pipet potential). (B) Current-voltage relations of SOC with Ba^{2+} and Ca^{2+} as charge carriers. The slope conductance was 0.7 pS for Ca^{2+} and 2.1 pS for Ba^{2+}, and the extrapolated reversal potential was 123 mV for Ca^{2+} and 63 mV for Ba^{2+} (adapted from Fig. 5B in Ref. 12 with permission). (C) Illustrating the change in $[Ca^{2+}]_i$ in the absence of TG (control), in the presence of TG (TG), and TG plus calphostin C (TG+Cal). $^*P < 0.05$, TG vs. control (adapted from Fig. 2B in Ref. 32 with permission, modified). (D) Illustrating reactivation of SOC by catalytic subunit of PKC (PKCc) plus ATP after excision rundown. Neither ATP alone nor heat-inactivated PKCc (inc PKCc) restored SOC activity after excision-induced rundown. $^*P < 0.05$, compared with corresponding after excision values (modified from Fig. 6B in Ref. 32 with permission).

Is SOC involved in the physiologic signaling pathway in MCs? Similar to vascular smooth-muscle cells, many vasoactive peptides in MCs induce Ca^{2+} signals through G-protein–coupled receptors that consequently activate PLC, resulting in production of IP_3 and DAG, the typical pathway for activation of SOC. It has been demonstrated that SOC was activated by Ang II, a physiologic stimulator, in human and rat MCs (33, 36). In addition to the G-protein–coupled receptor, receptor tyrosine kinase activation also results in opening of SOC. For instance, epidermal growth factor (EGF) elicited SOC-mediated single-channel currents and Ca^{2+} entry in cultured human MCs (31). Although the detailed intracellular signaling pathway remains unknown, receptor tyrosine kinase and PLC were required for the EGF-induced response (31, 33).

Similar to renal microvasculature, PKC might also be a key regulator of SOC activity in MCs. A series of studies from our laboratory demonstrated that thapsigargin-induced SOC activation was abolished by a specific PKC inhibitor, calphostin C (Fig. 2C, TG+Cal; Ref. 32). Activation of PKC or application of an active catalytic subunit of PKC into the bathing solution in the inside-out patches could mimic the thapsigargin-induced effects (Fig. 2D, PKCc). In a further study, we demonstrated that PKCα was the specific isoform of PKC for activating SOC (37). This finding was verified by Ahmmed *et al.* in endothelial cells, in which thrombin- or thapsigargin-induced CCE was markedly diminished by pharmacologic or genetic inhibition of PKCα (39). However, contradictory results have also been reported. In cultured human MCs, Menè *et al.* concluded that PKC was an inhibitor of SOC based on their findings that phorbol 12-myristate 13-acetate (PMA), an activator of PKC, inhibited Ang II–stimulated Ca^{2+} influx, assessed by microfluorometry (40). However, several concerns exist in that study. First, whether the Ca^{2+} entry they measured was mediated by SOC is uncertain because the Ang II–induced Ca^{2+}

influx was dependent on an increase in cytosolic Ca^{2+}, which is not a property of SOC. Second, whether the PMA-induced inhibition was specifically mediated by PKC activation is not verified. Nevertheless, the coupling signal between depletion of store and opening of SOC is a dilemma and whether or how PKC regulates SOC activity needs to be further investigated.

Canonical Transient Receptor Potential (TRPC) Proteins, Candidates of SOC in Renal Microvessels

Since the first observation of CCE, there has been intense debate regarding the molecular identity of SOC. Most attention has focused on the TRPC subfamily (15, 41). The TRP channel was first identified as an essential component of phototransduction in *Drosophila melanogaster* (42) and, later, was proposed to function as an SOC (43). The search for mammalian counterparts of TRP led to the discovery of a total of seven closely related genes encoding TRP channel proteins, termed TRPC1–TRPC7 (44). Contribution of TRPC proteins to store-operated Ca^{2+} entry has been substantiated by numerous studies (45–51).

A number of TRPC genes and proteins have been reported in vascular smooth muscle (5, 52, 53) and they might regulate myogenic tone or agonist-stimulated constriction of blood vessels (54–56). In freshly isolated rat renal preglomerular resistance vessels (interlobular arteries and afferent arterioles), TRPC1, TRPC3, TRPC4, TRPC5, and TRPC6 mRNAs and proteins were detected, whereas TRPC2 and 7 mRNAs were not expressed (57). However, as stated by the authors, it cannot be ruled out completely that these TRPC signals partially come from endothelial cells that might have also been present in the tissue sample preparation. Further experiments demonstrated that TRPC3 and TRPC6 protein levels were significantly greater (approximately 6- to 8-fold higher) than in the conduit vessel (aorta), implying that TRPC3 and TRPC6 may play an important role in mediating voltage-independent Ca^{2+} entry (store-operated or receptor-operated Ca^{2+} entry) in renal microcirculation. Using an isolated perfused kidney model, another group also exhibited the existence of TRPC1 protein in afferent and efferent arterioles, and suggested that TRPC1 protein might be the component mediating Ang II–induced constriction of efferent arteriole (58).

Expression of TRPC in Glomerular Cells

TRPC messengers and/or proteins have also been discovered in glomeruli and glomerular MCs by several independent groups. TRPC1, TRPC3, TRPC4, TRPC5, and TRPC6 proteins were identified in freshly isolated rat glomeruli (57). The localization of TRPC1, TRPC3, and TRPC6 in rat glomeruli was confirmed by a recent study, which demonstrated that TRPC1, TRPC3, and TRPC6 immunoreactivity was distributed identically and was predominantly confined to the glomerulus (59). However, no immunoreactivity for TRPC4, TRPC5, and TRPC7 was observed in glomeruli. Recently, we systematically examined the expression of TRPC isoforms in cultured human MCs and found that TRPC1, TRPC3, and TRPC4 were major isoforms in this type of cells (Fig. 3; Ref. 60). However, in mouse MCs, TRPC1 and TRPC4 are the only two TRPC messengers detected, and TRPC4 functions as an SOC (50). This discrepancy might be caused by species differences (human vs. mouse). Podocytes are specialized glomerular epithelial cells that surround the glomerular capillaries. Podocyte foot processes and the interposed glomerular slit diaphragm are essential components of the permeability barrier in the glomerulus. Most recently, Reiser *et al.* found that TRPC6 was expressed in podocytes and is a component of the glomerular slit diaphragm (61).

It seems that certain isoforms of TRPC proteins are selectively present in renal microcirculation and glomerular cells. What is lacking, in this scenario, are the function and physiologic relevance of these proteins. In addition, how the individual TRPC proteins interact to form a functional complex in the particular parts of kidney needs to be clarified, considering that TRPC isoforms can assemble to form homomers or heteromers (62–65).

Pathophysiologic Relevance of SOC in Renal Microcirculation and Glomerular Cells

The potential for disease associated with CCE is obvious, given the central role that this calcium influx pathway plays in so many physiologic systems. Accumulating evidence has demonstrated that impairment of SOC-mediated Ca^{2+} entry is involved in severe immunodeficiency (66, 67), acute pancreatitis (68), pulmonary hypertension (69, 70), and Alzheimer disease (71). As described previously, SOC mediates vasoconstrictor-induced responses in preglomerular resistance vessels. Regulation of preglomerular vasomotor tone ultimately controls glomerular filtration rate, sodium reabsorption, and systemic blood pressure. It is speculated that an alteration in SOC function will result in renal and cardiovascular disturbance. In freshly isolated single preglomerular vascular smooth-muscle cells from spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY), Fellner and Arendshorst demonstrated that the Ca^{2+} influx after depletion of internal Ca^{2+} stores with vasopressin-1 receptor agonist, ryanodine, or cyclopiazonic acid was doubled in SHR, indicating that store-operated Ca^{2+} entry is exaggerated in preglomerular vessels of SHR (72). It is unclear whether the enhanced store-operated Ca^{2+} entry led to hypertension or the high blood pressure resulted in upregulation of SOC expression or function. The same question also exists in pulmonary circulation (69, 70).

Growing evidence for association of SOC with glomerular diseases has emerged. Early diabetic nephropathy exhibits renal glomerular hyperfiltration and an increase in renal blood flow. The hyperfiltration is a dysfunctional state that may arise from a hyperglycemic-

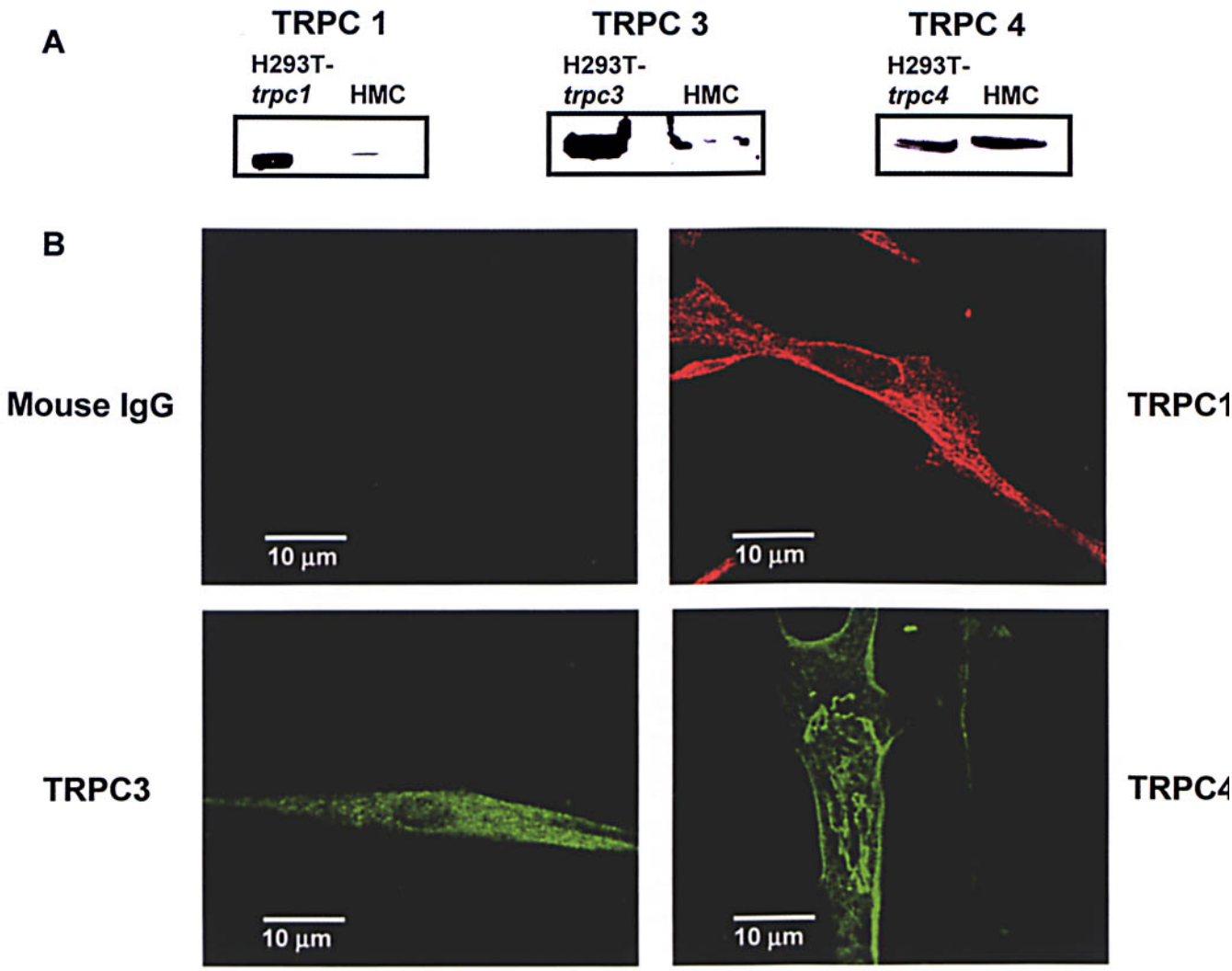

Figure 3. Western blot (A) and immunofluorescence (B) show the expression of TRPC1, TRPC3, and TRPC4 in human MCs (HMC). H293T-*trpc1*, or *trpc3*, or *trpc4* are *trpc1*, *trpc3*, or *trpc4* cDNA–transfected H293T cells, respectively, which served as corresponding controls.

induced hypocontractility of glomerular MCs that may be associated with depressed Ca^{2+} signaling events. In rat MCs cultured in high glucose to mimic the diabetic microenvironment, Menè *et al.* reported that store depletion–induced Ca^{2+} influx was significantly attenuated (73). The high glucose–inhibited CCE was normalized by a PKC inhibitor and mimicked by PMA, implying that a PKC mechanism was involved. Advanced glycation end products might also contribute to the blunted store-operated Ca^{2+} entry derived from high glucose (74). In contrast, another group argued against the downregulation of SOC activity by high glucose on the basis of their findings that thapsigargin-induced Ca^{2+} responses were not significantly different between the cells grown in normal and high glucose medium (35). The reasons for this discrepancy are unclear but the differences in cell passages and cell variability might be taken into account. Interestingly, although vasoconstrictor-stimulated Ca^{2+} entry of MCs is depressed under high-glucose condition, the basal Ca^{2+} influx might be potentiated (75). The high glucose–enhanced Ca^{2+} influx under the resting state was proposed to be mediated by SOC (75).

Adhesion of monocytes triggers apoptosis, cytotoxicity, cytokine release, and later proliferation of MCs, which are characteristics of glomerulonephritis. SOC might also contribute to early changes in intracellular Ca^{2+} concentration in MCs in response to monocyte adhesion (34). This conclusion is based on the study in which coculturing a monolayer of MCs and a cell suspension of a monoblastoid cell line (U 937) evoked a temporal elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in MCs, and this increase in $[Ca^{2+}]_i$ is dependent on extracellular Ca^{2+}. The authors speculated that the Ca^{2+} influx was mediated by SOC because VOCC was hardly detectable in their monolayer cultures. However, studies that are more careful and more thorough are required to confirm their conclusion.

An exciting study reported by Reiser *et al.* recently established a molecular link between TRPC6 and autosomal dominant focal segmental glomerular sclerosis (FSGS; Ref.

61). Using immunofluorescence and immunoelectron microscopy, they found that TRPC6 is enriched in podocytes and is found in podocyte foot processes near the slit diaphragm. Immunoprecipitation studies showed that TRPC6 interacts physically with nephrin and podocin, two essential structural and functional constituents of the slit diaphragm–signaling platform (76–78). They screened 16 additional families with FSGS and identified 5 different TRPC6 mutations associated with disease. Using whole-cell patch clamp, Reiser *et al.* demonstrated that two of the mutant TRPC6 have larger current amplitudes after receptor stimulation than wild-type TRPC6. Their findings are consistent with an earlier study by Winn *et al.*, who identified a family with autosomal dominant FSGS that segregated with a point mutation in the TRPC6 gene (79). The involvement of TRPC6 mutations in FSGF certainly sheds new light on the pathogenesis of renal failure, which is a genetically and clinically heterogeneous group of disorders.

Conclusion

Convincing data demonstrate that SOC and the candidates of its molecular entity, TRPC proteins, exist in renal microvessels and glomeruli. Store-operated Ca^{2+} entry takes part in Ca^{2+} responses after stimulation of the contractile cells by vasoconstrictors. Therefore, it is not surprising that SOC plays a fundamental role in controlling renal microcirculation and glomerular hemodynamics. Perturbations in the SOC function in the particular regions of the kidney will have the potential for pathologic outcomes, such as diabetic nephropathy. Meanwhile, planned pharmacologic manipulations may find clinical usefulness in these disease states. In this sense, the goal of developing specific drugs targeted to SOC in the renal microvasculature and glomeruli may, for the first time, be a real possibility.

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