Molecular Pharmacology Fast Forward. Published on July 27, 2006 as doi: 10.1124/mol.106.029280
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MOL 29280

TRPC1 and Caveolin-1: Good Friends in Tight Spaces

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Molecular Pharmacology Fast Forward. Published on July 27, 2006 as DOI: 10.1124/mol.106.029280
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MOL 29280

Running title: CSD regulates TRPC1 function

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Molecular Pharmacology Fast Forward. Published on July 27, 2006 as DOI: 10.1124/mol.106.029280
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Abstract

Caveolae formation has raised the concept of energy efficiency to new heights. The ultimate purpose of caveolae formation is to colocalize signaling proteins with membrane microdomains in order to facilitate their interaction and improve signal transduction efficiency. While we know that the main structural protein of caveolae is caveolin, it is unclear how caveolin interacts with membrane proteins to facilitate their integration into lipid raft domains. A caveolin-scaffolding domain (CSD) on caveolin itself can associate with membrane proteins such as G proteins and endothelial nitric oxide synthase. In this issue, Kwiatek et al. report that the TRPC1 channel protein contains a C-terminal CSD-consensus binding sequence that allows for its physical and functional interaction with caveolin-1 in the caveolae of human pulmonary artery endothelial cells (PAEC). Competitive interaction with a CSD-conjugated peptide attenuates thrombin- and thapsigargin-induced Ca^{2+} influx via store-operated TRPC1 channels. Their data suggest that caveolin-1 can directly regulate TRPC1 function, extending its already ascribed role as a structural protein.

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In this day and age of energy crises, it seems that we are all scrambling to be more efficient and to use our resources wisely. As it turns out, our cells have been doing so on their own for a long time, as we are just now discovering, by colocalizing receptors, signaling proteins and effectors within cellular microdomains. Caveolae are cholesterol- and sphingolipid-rich flask-shaped invaginations of the plasma membrane, whose principal structural component is caveolin (Schlegel et al., 2000). In the vasculature, caveolae appear to be more prominent in endothelial cells than in smooth muscle cells (Gabella and Blundell, 1978), although the number of caveolae and expression level of caveolin can be significant increased in smooth muscle cells in patients with certain vascular diseases, such as idiopathic pulmonary arterial hypertension (Patel et al., 2005) The 'simplest' physiological role of caveolae and caveolin is to centralize, concentrate and colocalize cooperative receptors, signaling molecules/proteins and effectors within microdomains (Carver and Schnitzer, 2003; Cohen et al., 2004). G protein-coupled receptors (GPCR), heterotrimeric G proteins, receptor tyrosine kinases (RTK), Rho-1, calmodulin, VAMP-2 syntaxin, ezrin, NHEFR, Z01, Rac-1, stathmin, SNARE proteins, adenylyl cyclase, PI_3K, phospholipase C (β and γ), cytoskeletal protein 4, endothelial nitric oxide synthase (eNOS), and ion channels are examples of the signaling proteins and molecules known to co-exist with caveolin in caveolae (Ambudkar, 2006; Beech, 2005; Brazer et al., 2003; Cioffi et al., 2005; Lockwich et al., 2000; Ostrom et al., 2002; Swaney et al., 2006).

Transient receptor potential (TRP) channels have recently been reported to localize within caveolae, particularly the canonical TRPC1, TRPC3, and TRPC4 isoforms (Brazer et al., 2003; Lockwich et al., 2001; Nilius et al., 2003; Torihashi et al., 2002; Uehara, 2005). TRPC1 also coimmunoprecipitates with caveolin-1 (cav-1), one of the three caveolin isoforms (Bergdahl et al., 2003; Lockwich et al., 2000), even more suggestive that it exists within caveolae. TRPC1,

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TRPC3, and TRPC4 isoforms are believed to be components of native store-operated Ca^{2+} channels (SOC) in many vascular smooth muscle cell types (Freichel et al., 2001; Inoue et al., 2006; Kunichika et al., 2004; Lin et al., 2004; Wang et al., 2004; Wang et al., 2006; Xu and Beech, 2001). TRPC1 in particular appears to be involved in SOC function in pulmonary artery endothelial cells (PAEC) (Alvarez et al., 2005; Bergdahl et al., 2003; Cioffi et al., 2005; Jho et al., 2005).

The presence of TRPC1 in these caveolar lipid raft domains seems to constitute an important factor in its function as an SOC. A number of studies have shown that disruption of caveolae, such as by methyl-β-cyclodextrin (MβCD), significantly inhibits SOC-mediated capacitative Ca^{2+} entry (CCE) (Bergdahl et al., 2003; Brownlow et al., 2004; Kunzelmann-Marche et al., 2002; Lockwich et al., 2000; Patel et al., 2006). Since depletion of inositol-1,4,5-trisphosphate (IP_3)-sensitive endoplasmic reticulum (ER) or sarcoplasmic reticulum (SR) Ca^{2+} stores is required for activation of SOC (Parekh, 2003), these findings imply that caveolae formation somehow enhances the interaction between the ER/SR and SOC channels.

While the primary role of cav-1 is as a structural protein, it also helps localize TRPC1 to the plasma membrane itself (Ambudkar et al., 2004). Therefore, TRPC1 and cav-1 must physically interact. Brazer et al. (2003) previously showed that TRPC1 is assembled in a complex with cav-1 and that the N-terminus of TRPC1 (amino acids 271-349) contains a cav-1 binding motif (CBM) between amino acids 322 and 349 (Brazer et al., 2003). Deletion of this binding domain suppresses SOC function and inhibits CCE without altering localization of TRPC1 to the plasma membrane.

So how exactly does cav-1 regulates SOC function or functionally interacts with SOC? The *Caveolae Signaling Hypothesis* (Schlegel et al., 2000) extends the role of caveolae beyond

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that of clustering signaling proteins within microenvironments to include an active role for cav-1 itself in regulating signal transduction. According to this theory, cav-1 interacts with and regulates the activity of caveolae-associated signaling proteins (e.g., GPCR, eNOS, Src) via a 20 amino-acid residue (aa. 82-101) caveolin scaffolding domain (CSD). In most cases, interaction with the CSD of cav-1 either maintains the signaling protein in an inactive state until a stimulus is presented, or it terminates signal transmission after activation (Drab et al., 2001; Gratton et al., 2000; Murthy and Makhlouf, 2000). The CSD is critical for caveolin homo-oligomerization, and for the interaction of caveolin with caveolae-associated proteins such as G proteins, H-Ras, Src family tyrosine kinases, and, as described below, TRPC1 channels (Couet et al., 1997; Kwiatek et al., 2006; Li et al., 1996)

In this issue, Kwiatek et al. (2006) elaborate upon the findings of Brazer et al. (2003) and demonstrate a role for cav-1 in regulating not only TRPC1 localization, but also its function via interaction with the CSD domain of cav-1 (Fig. 1). The present data show that introduction of a competitive-binding CSD peptide attenuates thrombin- and thapsigargin-induced Ca^{2+} influx through SOC in human PAEC. Furthermore, they identify a 9-amino acid domain in the C-terminus (aa. 781-789) of TRPC1 that acts as a CSD binding sequence (Fig. 1A). Introduction of a synthetic CSD binding sequence within the C-terminus of TRPC1 significantly decreased thrombin-induced Ca^{2+} influx. This finding contrasts with that of Brazer et al. (2003), who suggested that cav-1 binds only to an N-terminal cav1-binding motif (CBM; aa 322-349) of TRPC1 (Fig. 1A). However, truncation of cav-1 (i.e., removal of CSD, membrane anchoring domain, and palmitoylation sites) significantly decreased CCE and membrane expression of both TRPC1 and cav-1 in that study (without disturbing caveolae formation) (Brazer et al., 2003). These data suggest that *a*) cav-1 may interact with TRPC1 via multiple domains, including,

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perhaps, the N-terminal CBM (cav1 binding motif) (Brazer et al., 2003) and the C-terminal CSD demonstrated by Kwiatek et al. (2006), *b*) cav-1 anchoring within membrane lipid raft domains is required for superior TRPC1 function, *c*) how cav1 interacts with TRPC1 (or via which binding domains) depends on different signaling cascades, and *d*) cav-1 binding to different binding domains in TRPC1 may be selectively regulated by store depletion-mediated signals (for opening SOC) and receptor-activated signals (for opening ROC). In addition, Kwiatek et al. (2006) suggest that cav-1 phosphorylation via Src activation by thrombin is altered by the CSD peptide without altering SR Ca^{2+} release or TRPC1-mediated CCE. Therefore, the role of cav-1 phosphorylation in these cells is limited to its involvement in caveolae-mediated endocytosis as the authors had previously found (Minshall et al., 2000).

The findings suggest that the function of ion channels such as TRPC1 is directly regulated by the physical interaction with the CSD domain of cav-1 (Fig. 1B). However, while Kwiatek et al. describe a role for cav-1, other studies have also implicated cytoskeletal proteins in the regulation of TRPC function. Tang et al. (2000) showed that TRPC4 interaction with a PDZ domain on the Na^{+}-H^{+} exchange regulatory factor (NHERF) facilitates interaction with phospholipase C-β (Tang et al., 2000). Rosado & Sage (2000) demonstrated the requirement for actin cytoskeleton remodeling to permit coupling between IP_3 type II receptors and TRPC1 channels in platelets. Similarly, actin stabilization is required to prevent internalization of TRPC3 channels and loss of CCE (Lockwich et al., 2001; Mery et al., 2002) identified a C-terminal PDZ domain in the TRPC4 sequence which is required for its localization to the plasma membrane. Finally, Cioffi et al. (2005) recently showed that activation of SOC channels in PAEC requires interaction of TRPC4 channels with cytoskeletal protein 4.1 (Cioffi et al., 2005). These observations indicate that TRPC channel proteins not only interact with caveolin to

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localize in caveolae, but also interact with a variety of proteins and molecules that ensure the function and regulation of the TRPC-encoded SOC. The interaction of cav-1 and TRPC1 may begin in the endoplasmic (ER) or sarcoplasmic (SR) reticulum and Golgi apparatus where proteins are synthesized, modified (e.g., glycosylated) and finalized (e.g., correctly folded) before their trafficking or insertion onto the plasma membrane.

TRPC-mediated Ca^{2+} influx into the cytosol of PAEC, such as that provoked by thrombin (Fig. 1B), is one of the main causes of endothelial cell contraction, which regulates intercellular gaps between endothelial cells and alters endothelial permeability (or barrier function). In addition to endothelial shortening and migration, the newly introduced Ca^{2+} can provoke changes in gene expression within PAEC, an effect that can alter not only PAEC function, but also pulmonary artery smooth muscle cell function via paracrine mechanisms. By binding with cav-1 in both N- and C-termina, TRPC1 can be efficiently regulated upon activation of receptors. As shown in Figure 1B, accumulated ligand (or, in this case, thrombin) in caveolae activates the receptors (GPCR or RTK) located in caveolae and increase synthesis of IP_3 and diacylglycerol. By binding with IP_3 receptors (IP_3R) on the ER/SR membrane, the second messenger IP_3 induces a transient increase in $[Ca^{2+}]_{cyt}$ due to Ca^{2+} release from the ER/SR to the cytosol. Opening of the Ca^{2+} release channels or IP_3R is an efficient way to deplete Ca^{2+} from the intracellular stores (i.e., ER or SR). The store depletion then activates TRPC-encoded SOC, which are located in caveolae, and promote Ca^{2+} influx or causes CCE. Since TRPC channels are also highly permeable to Na^+, the local accumulation of intracellular Na^+ would then activate the reverse mode of Na^+/Ca^{2+} exchange (Rosker et al., 2004) and further enhance Ca^{2+} entry (Fig. 1B). The proximity of the receptor, the channel, the transporter and the caveolin allows the ligand-mediated increase in $[Ca^{2+}]_{cyt}$ to be efficiently and rapidly regulated for signal transduction and

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for stimulating functional changes of the cell.

In summary, the data from Kwaiatek et al. (2006) offer up another facet of ion channel regulation by a protein known more for its architectural role than for its regulatory function. The evidence is clear that caveolin-1 not only localizes TRPC1 to caveolae, but that its physical (and functional) interaction with TRPC1 via the caveolin-scaffolding domain regulates channel function and subsequent thrombin-induced CCE in human PAEC. The functional interaction among all the proteins and molecules in caveolae provides a well-coordinated and precisely controlled mechanism to facilitate the transduction of external signals to the cell.

Acknowledgments

The authors apologize for the investigators whose work is not included in the diagram and cited in the review because of page limitations.

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Footnotes

This work is supported by the NIH grants (HL 064945, HL 054043 and HL 066012).

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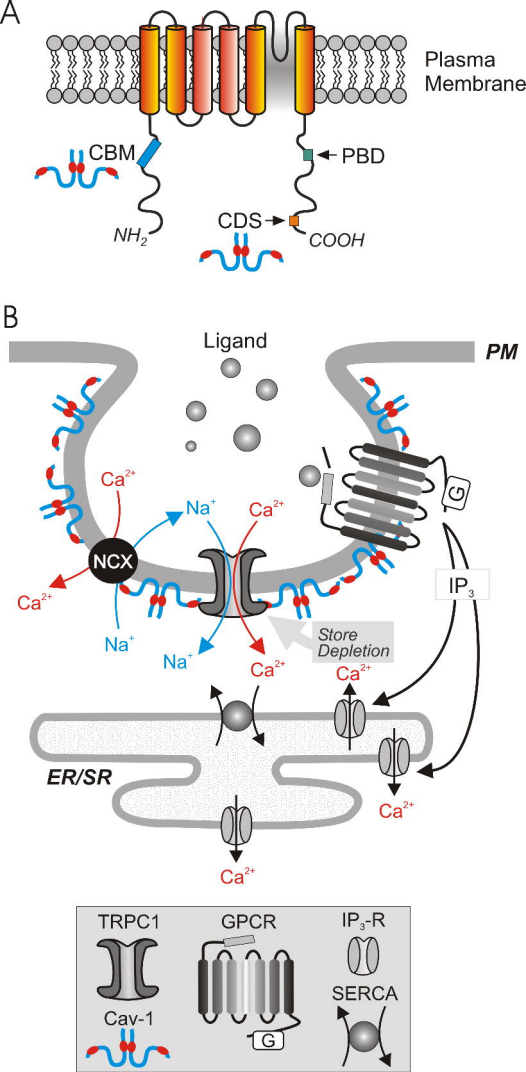
Figure Legend

Figure 1. Schematic diagram depicting the caveolin-1 binding domains in TRPC1 (A) and the potential mechanisms (B) that are involved in ligand- or thrombin-mediated regulation of intracellular $[Ca^{2+}]_{cyt}$. CBM, cav1 binding motif; PBD, protein 4 binding domain; CSD, caveolin-scaffolding domain; PM, the plasma membrane; ER/SR, endoplasmic reticulum and sarcoplasmic reticulum; NCX, Na^{+}/Ca^{2+} exchanger; G, G protein; GPCR, G protein-coupled receptor; IP_3, inositol 1,4,5-trisphosphate; IP_3R, IP_3 receptor; SERCA, the SR/ER Ca^{2+}-Mg^{2+} ATPase; Cav-1, caveolin-1.


A
Plasma Membrane
CBM
PBD
CDS
NH_2
COOH
B
Ligand
PM
Ca^{2+}
Na^+
NCX
G
IP_3
Store Depletion
ER/SR
TRPC1
GPCR
IP_3-R
Cav-1
SERCA