Presenilin 2 Interacts with Sorcin, a Modulator of the Ryanodine Receptor*

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Perturbed Ca²⁺ homeostasis is a common molecular consequence of familial Alzheimer’s disease-linked presenilin mutations. We report here the molecular interaction of the large hydrophilic loop region of presenilin 2 (PS2) with sorcin, a penta-EF-hand Ca²⁺-binding protein that serves as a modulator of the ryanodine receptor intracellular Ca²⁺ channel. The association of endogenous sorcin and PS2 was demonstrated in cultured cells and human brain tissues. Membrane-associated sorcin and a subset of the functional PS2 complexes were co-localized to a novel subcellular fraction that is distinctively positive for calcineurin B. Sorcin was found to interact with PS2 endoproteolytic fragments but not full-length PS2, and the sorcin/PS2 interaction was greatly enhanced by treatment with the Ca²⁺ ionophore A23187. Our findings reveal a molecular link between PS2 and intracellular Ca²⁺ channels (i.e. ryanodine receptor) and substantiate normal and/or pathological roles of PS2 in intracellular Ca²⁺ homeostasis.

Naturally half of early-onset familial Alzheimer’s disease (FAD) is associated with mutations in genes encoding two homologous proteins, presenilin 1 (PS1) and presenilin 2 (PS2) (1). Recent studies have shown that PS1 (and perhaps PS2) plays an essential role in the γ-secretase cleavage of amyloid β-protein precursor (2–4) and the trafficking/maturation of other select cellular proteins, including Notch and TrkB (5–8). Common molecular consequences of presenilin FAD mutations include the increased production of amyloid β-peptide x-42 and increased apoptosis (reviewed in Refs. 9–11). In addition, FAD mutations in both PS1 and PS2 have been shown to disrupt intracellular Ca²⁺ homeostasis (12, 13). However, the mechanism by which Ca²⁺ dyshomeostasis contributes to FAD pathogenesis is still unresolved.

Recently, a number of molecules that form complexes with the presenilins have been identified, including β- and δ-catenin (14–19), p0071 (20), amyloid β-protein precursor (21), filamin/Fh-1 (22), Notch (23), GSK3β (24), Rab11 (25), calsenilin (26), calmyrin (27), QM/Jif-1 (28), and Bel-XL (29). It is currently unclear whether these interactions mediate pathogenesis in presenilin FAD. It is also noteworthy that some of these proteins have been shown to interact either preferentially or exclusively with full-length presenilin over the N- or C-terminal fragments. Since only a subset of presenilin proteins are cleaved to form stable, functional presenilin complexes (30–35), and the remaining full-length proteins are degraded by the proteasome (32, 36–38), proteins that interact with the N- and/or C-terminal presenilin fragments are more likely to mediate presenilin function as opposed to maturation of the presenilins. Additionally, many of these presenilin-interacting proteins have been identified and characterized using overexpression in cell systems, whereas only a few have been demonstrated to interact with PS1 and/or PS2 endogenously (e.g. β-catenin).

Although the N-terminal and loop domains are not conserved between the presenilins, FAD mutations have been identified within these regions in both proteins (1). We have identified the protein sorcin as a PS2 loop-interacting molecule. Sorcin is a penta-EF-hand Ca²⁺-binding protein that modulates the ryanodine receptor (RyR) intracellular calcium channel (39–43) and has previously been shown to be co-localize with brain RyR in the rat caudate-putamen nucleus (44). We have found that sorcin interacts with the stable C-terminal endoproteolytic fragment of PS2 but not with the immature full-length form. This interaction between sorcin and a subset of the functional PS2 complexes was modulated by Ca²⁺ and occurred in a novel subcellular fraction. Our results reveal a molecular link between PS2 and intracellular Ca²⁺ channels, suggesting that sorcin is involved in the role of PS2 in intracellular Ca²⁺ homeostasis.

EXPERIMENTAL PROCEDURES

Expression Constructs—Molecular cloning of cDNAs encoding sorcin (40) and granulin (45) from an adult human brain cDNA library was performed using a Marathon-ready rapid amplification of cDNA ends kit (CLONTECH). Isolated full-length cDNAs were subcloned into the pcDNA3.1/myc-His mammalian expression vector (Invitrogen), and the inserts were sequenced using a double-stranded DNA cycle sequencing system (Life Technologies, Inc.). Inducible expression constructs (pUHD10–3) coding for wild-type and N141I mutant versions of PS2 were previously described (32). For the constitutive expression of PS2, the inserts from the inducible expression constructs (without FLAG epitope tags) were subcloned into pcDNA3.1/Zeo(+) (Invitrogen) and were fully verified by sequencing.

Generation of Stable PS2 Cell Lines—Stable PS2 cell lines were generated by transfecting SH-SYSY cells in a 100-mm dish with 5 μg of
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RESULTS

Identification of Sorcin as an Interactor for the Large Hydrophilic Loop Region of PS2—To search for putative interacting proteins for the PS2 loop region, we performed a domain-specific homology search of GenBank®. The protein synexin was found to have a high degree of homology between its N terminus of the annexin family of calcium- and phospholipid-binding proteins (50). We then asked whether the protein sorcin, which has previously been shown to interact with the N-terminal region of synexin (47), might also interact with the PS2 loop. Sorcin is a member of the family of Ca2+-binding proteins harboring five EP-hand motifs (40, 41). We first isolated full-length sorcin cDNA from an adult human brain library and subcloned it into an expression plasmid encoding Myc epitope tag; Myc-tagged sorcin (Myc-sorcin) was then stably transfected into human neuroblastoma SH-SY5Y cells (Fig. 1B). Western blot analysis using anti-Myc antibody revealed Myc-sorcin with an apparent molecular mass of 29 kDa, and anti-sorcin antibodies detected a ~29-kDa transgene-derived epitope-tagged form of sorcin as well as the 26-kDa endogenous sorcin (Fig. 1B). We next performed complementary co-immu-

FIG. 1. Identification of sorcin as an interactor for the large hydrophilic loop region of PS2. A, homology between the large hydrophilic loop domain region of PS2 and the N-terminal region of synexin. Amino acids 319–347 of human PS2 are compared with amino acids 17–56 of human synexin. Identical residues are indicated by straight lines and similar residues are indicated by a + between the sequences. B, expression and detection of sorcin in stable sorcin cell lines. Human neuroblastoma SH-SY5Y cells were stably transfected with either empty vector (vector) or a Myc-tagged sorcin expression construct (myc-sorcin). The cell lysates were analyzed by Western blot analyses using anti-Myc (left) or polyclonal anti-sorcin (right) antibodies. C, identification of the interaction between sorcin and PS2 using co-immunoprecipitation of Myc-tagged sorcin and the endogenous PS2 C-terminal fragment (PS2-CTF). Detergent lysates from COS cells that were transiently transfected with the constructs indicated in the upper panel were immunoprecipitated with αPS2Loop and were analyzed by Western blotting using anti-Myc antibody. Myc-tagged sorcin that co-immunoprecipitates with endogenous PS2-CTF is indicated by an arrow. D, detection of sorcin in human neuroblastoma cells and brain using combined immunoprecipitation-Western blot analyses. Detergent lysates were prepared from cultured native SH-SY5Y cells (left) or human temporal cortex (right), and samples were subjected to immunoprecipitation with either pre-immune sera or polyclonal anti-sorcin antibodies and then analyzed by Western blotting with monoclonal anti-sorcin antibodies. E, co-immunoprecipitation of sorcin and PS2-CTF in human brain extracts. Temporal cortex tissues from neurologically normal patients were homogenized, lysed in the presence of 0.5% Nonidet P-40, and subjected to immunoprecipitation using αPS2Loop, with αPS1Loop used as a control antibody. Immunoprecipitates were then analyzed by Western blotting using polyclonal anti-sorcin antibody. Representative data from five independent experiments are shown.

Subcellular Fractionation—Subcellular fractionation of cultured cells was performed using a protocol that has been previously described with minor modifications (48, 49). Cells were washed twice each with ice-cold phosphate-buffered saline and homogenization buffer (10 mM triethanolamine, 10 mM acetic acid, 250 mM sucrose, 1 mM EDTA, and 1 mM diethiothreitol) plus protease inhibitor mixture (Roche Molecular Biochemicals) and homogenized using a 25-gauge needle and a tight-fitting Dounce homogenizer. A post-nuclear supernatant resulting from low speed centrifugation was separated by differential centrifugation at 1,000 × g, 14,000 × g, and 100,000 × g to yield post-nuclear supernatant, P2, and P3, respectively. Pooled membrane fractions were further separated by density gradient centrifugation using step gradients consisting of 24, 19, 13, 14.66, and 10% isotonic Nycodenz solutions (made in 0.75% NaCl, 10 mM Tris (pH 7.4), 3 mM KCl, and 1 mM EDTA) and were fractionated using a density gradient fractionator. The fractions were then analyzed by Western blotting using antibodies to PS2, sorcin, and other marker proteins.

Each plasmid: wild-type PS2, N141I PS2, or vector alone (pcDNA3.1/Zeo+). Individual zeocin-resistant colonies were isolated and screened for PS2 expression by Western blotting using αPS2Loop (30) and αG2L (46). Stable cell lines were maintained in the presence of 250 µg/ml Zeocin (Invitrogen) as described previously (32).

Western Blot Analyses, and Immunoprecipitation—Protein quantitation, SDS-polyacrylamide gel electrophoresis (4–20 or 30%) at 1:2500; and polyclonal anti-sorcin (47) at 1:10,000. To quantitate relative amounts of presenilin and sorcin in the blots, Fluor-S MultiImager MultiAnalyst software (Bio-Rad) were utilized. Cells or tissues were lysed using IP buffer (10 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1% Triton X-100, 0.25% Nonidet P-40, 2 mM EDTA) plus protease inhibitors, and solubilized proteins were subjected to immunoprecipitation. For the co-immunoprecipitation experiments, 0.25–0.5% Nonidet P-40 was utilized, and 0.1% bovine serum albumin was included. The samples were pre-cleared with protein A conjugated with magnetic beads (PerSeptive Diagnostics) for 1 h at 4 °C, incubated with antibodies overnight, further incubated with protein A-magnetic beads (30 µl/sample) for 2 h at 4 °C, and washed three times with IP buffer. Immunoprecipitates were collected using a magnetic bead collector, heated to 60 °C in sample buffer, and subjected to SDS-polyacrylamide gel electrophoresis and Western blotting. Antibodies used include GM130 (Transduction Laboratories), calnexin (Stressgene), transferrin receptor (a gift of Dr. I. Trowbridge), APS26 (15) (a gift of Anke Diehlmann and Konrad Beyreuther), and calcineurin B (Santa Cruz Biotechnology).

Confocal Microscopy—Cells grown on glass coverslips or chamber slides were fixed (4% paraformaldehyde), double-stained with monoclonal anti-annexin antibody and αPS2Loop, and then incubated with Cy3-conjugated anti-mouse secondary antibodies (Jackson Laboratories) and Bodipy-conjugated anti-rabbit secondary antibodies (Molecular Probes). Fluorescent images were captured and analyzed using a Bio-Rad 1024 confocal microscope mounted on a Nikon inverted microscope.

Subcellular Fractionation—Subcellular fractionation of cultured cells was performed using a protocol that has been previously described with minor modifications (48, 49). Cells were washed twice each with ice-cold phosphate-buffered saline and homogenization buffer (10 mM triethanolamine, 10 mM acetic acid, 250 mM sucrose, 1 mM EDTA, and 1 mM diethiothreitol) plus protease inhibitor mixture (Roche Molecular Biochemicals) and homogenized using a 25-gauge needle and a tight-fitting Dounce homogenizer. A post-nuclear supernatant resulting from low speed centrifugation was separated by differential centrifugation at 1,000 × g, 14,000 × g, and 100,000 × g to yield post-nuclear supernatant, P2, and P3, respectively. Pooled membrane fractions were further separated by density gradient centrifugation using step gradients consisting of 24, 19, 13, 14.66, and 10% isotonic Nycodenz solutions (made in 0.75% NaCl, 10 mM Tris (pH 7.4), 3 mM KCl, and 1 mM EDTA) and were fractionated using a density gradient fractionator. The fractions were then analyzed by Western blotting using antibodies to PS2, sorcin, and other marker proteins.
noprecipitation analyses of PS2 and Myc-sorcin using aPS2Loop antibody (30) in lysates prepared from COS cells transfected with either Myc-sorcin or a Myc-tagged control protein, Myc-grancalcin, or Myc-XIAP (Fig. 1C). Only Myc-sorcin was co-immunoprecipitated by aPS2Loop, indicating that Myc-sorcin interacts with endogenous PS2 C-terminal (loop) fragments (PS2-CTF) (Fig. 1C).

Sorcin was detectable in human temporal cortex by combined immunoprecipitation-Western blotting analyses using two separate antibodies raised against human sorcin (Fig. 1D). Sorcin in the human temporal cortex (~28 kDa) exhibited a slightly larger apparent molecular mass than sorcin in SH-SY5Y cells (~26 kDa), possibly due to alternative splicing; a molecular mass of ~26–28 kDa is also slightly larger than the previously reported ~22 kDa (39, 40). To determine whether this endogenous sorcin associates with endogenous PS2 in vivo, detergent lysates were prepared from human temporal cortex and subjected to co-immunoprecipitation using aPS2Loop antibody or

**Fig. 2. Subcellular localization of the sorcin-PS2 complex.** A, immunofluorescence confocal microscopy of sorcin and PS2. Stable SY5Y cell lines expressing wild-type PS2 were fixed, permeabilized, and double-labeled with either monoclonal anti-sorcin antibody (red, Cy3) or aPS2loop (green, Bodipy). B, subcellular distribution of sorcin in cytosolic and membrane subcellular fractions. Wild-type PS2 stable SH-SY5Y cells were subjected to cell fractionation and differential centrifugation to yield post-nuclear supernatant (PNS), cytosol, and heavy (P2, 14,000 × g) and light (P3, 100,000 × g) membrane fractions. Equal amounts of protein from each subcellular fraction were analyzed by Western blotting using monoclonal anti-sorcin antibody or aPS2Loop. C, subcellular distribution of the sorcin-PS2 complex in density gradient subcellular fractions. Total membrane fractions from stable SY5Y cells expressing wild-type PS2 were separated on a discontinuous NycoDenz gradient. Fractions were collected from the top using a density gradient fractionator. Equal volumes of each fraction were analyzed by Western blotting using aPS2loop, monoclonal anti-sorcin antibody, anti-calcineurin B, and APS26 (anti-PS2 NTF, where NTF is N-terminal fragment) as well as antibodies to known subcellular organelle markers, including calnexin, GM130, and transferrin receptor (Tf-R). Representative data from three independent experiments are presented.
with αPS1 Loop (30) as a negative control (Fig. 1E). Endogenous sorcin was recovered from these samples using only αPS2 Loop (Fig. 1E), indicating that sorcin associates with PS2 but not with PS1 in the brain.

**Subcellular Localization of the Sorcin-PS2 Molecular Complex**—To explore the cellular function of the PS2/sorcin interaction, we next attempted to determine the subcellular locus wherein the PS2/sorcin interaction occurs. For this purpose, we first visualized sorcin and PS2-CTF in stable SH-SY5Y cell lines using double immunofluorescence confocal microscopy (Fig. 2A). PS2 immunoreactivity was mainly detected in smooth ER/Golgi-like intracellular membrane compartments, whereas sorcin immunoreactivity was more dispersed (Fig. 2A). Sorcin and PS2-CTF co-localized only to a restricted subcellular region (Fig. 2A, yellow indicates overlying signals). Since sorcin is a cytosolic protein (51) and PS2 is a known integral membrane protein (52), we predicted that a subset of cytosolic sorcin might associate with membranous subcellular structures to allow the interaction of sorcin with PS2. To locate the PS2-sorcin interaction, we performed subcellular fractionation using stable PS2 SH-SY5Y cell lines. After an initial homogenization and differential centrifugation, sorcin was predominantly found in the cytosolic fraction, although sorcin immunoreactivity was also detectable in the heavy membrane fraction, P2 (Fig. 2B). As predicted, PS2-CTF was absent in the cytosolic fraction and was highly enriched in the P2 fraction, where membrane-associated sorcin was detected (Fig. 2B).

To define the specific subcellular membrane compartment where the PS2/sorcin interaction occurs, total membrane fractions prepared from SH-SY5Y stably cells expressing wild-type PS2 were further separated using Nycodenz discontinuous density gradient centrifugation (48, 49). Each fraction was analyzed by Western blotting using antibodies to PS2 and sorcin (Fig. 2C). The full-length PS2 polypeptide exhibited virtually identical subcellular distribution to that of calnexin, a rough ER marker (arrow a, Fig. 2C). In contrast, the PS2-CTF was visualized in three major peaks: peak one (fractions 3 and 4), peak two (fractions 6–8), and peak three (fractions 11 and 12) (Fig. 2C). Sorcin and PS2 were co-localized only to peak one membrane fractions, indicating that the PS2-sorcin complex was localized specifically to this subcellular compartment (arrow b, Fig. 2C). In addition, we performed Western blot analyses using antibodies to multiple subcellular marker proteins. Interestingly, 19-kDa calcein B, a Ca^{2+}-binding subunit of calceinun, was distinctively co-distributed with sorcin in the Nycodenz gradient fractions (Fig. 2C). Membrane-associated sorcin did not appear to co-localize with the majority of other subcellular markers tested, including α-adapnin, γ-adapnin, clathrin light chain, BAG-1, and Bcl-2 (data not shown). Neither the Golgi matrix protein GM130 nor the transferrin receptor co-distributed with sorcin or PS2 (Fig. 2C). These data demonstrate that membrane-associated sorcin and a subset of PS2 endoproteolytic fragments, but not full-length PS2, co-localize together to a subcellular compartment that is positive for calcein B. Our data also indicate that the C-terminal endoproteolytic fragment and full-length forms of PS2 localize to different subcellular compartments in SH-SY5Y cells (Fig. 2C).

**Sorcin Associates with the PS2 Endoproteolytic C-terminal Fragment but Not with Full-length PS2**—To determine further the PS2 species that predominantly interacts with sorcin, we co-immunoprecipitated PS2 using anti-sorcin antibodies (Fig. 3A). The levels of PS2-CTF that co-immunoprecipitated with endogenous sorcin were proportional to the levels of PS2-CTF detected in total cell lysates (data not shown). Virtually no full-length PS2 was recovered in the sorcin immunoprecipitates, confirming that sorcin preferentially interacts with PS2-CTF (Fig. 3A).

We next tested whether increased accumulation of full-length PS2 affects the interaction between sorcin and PS2. Both treatment with the proteasome inhibitors MG132 or ALLN (Fig. 3B) and overexpression of PS2 by transient transfection (data not shown) have previously been shown to lead to increased levels of full-length PS2 and ubiquitin-positive high molecular weight forms of PS2 but not PS2 endoproteolytic fragments (32, 53). No increase was observed in the interaction between PS2 and sorcin under either condition. Along with the subcellular fractionation data, our studies reveal that sorcin...
interacts with a subset of the PS2 complexes consisting of the endoproteolytic fragments but does not interact with full-length PS2.

Elevated Intracellular Calcium Enhances the Sorcin/PS2 Interaction and Translocation of Sorcin to the Membrane—We next examined whether increasing the cytosolic Ca\(^{2+}\) concentration modulates the sorcin/PS2 interaction. Treatment with the Ca\(^{2+}\) ionophore A23187 did not alter the steady-state levels of sorcin or PS2 (Fig. 4A). Meanwhile, the level of sorcin that co-immunoprecipitated with PS2Loop greatly increased as the result of A23187 treatment (Fig. 4A). To explore the possibility that Ca\(^{2+}\) mediates the translocation of the sorcin-PS2 complex, we examined the subcellular distribution of membrane-associated sorcin in PS2-expressing cells that were grown in the presence or absence of A23187. Although A23187 did not alter the subcellular distribution of the sorcin-PS2 complex, we found that A23187 treatment led to increased association of sorcin with the membrane (Fig. 4B). Our studies demonstrate that sorcin is translocated from the cytosol to the membrane when cytosolic Ca\(^{2+}\) is elevated by this ionophore, indicating that the recruitment of sorcin into a molecular complex harboring PS2 is modulated by intracellular Ca\(^{2+}\) levels.

DISCUSSION

We report that presenilin 2 interacts endogenously with sorcin, a modulator of the RyR intracellular Ca\(^{2+}\)-releasing channel. Regulation of ryanodine receptor activity by accessory molecules has been implicated in synaptic plasticity and other neuronal activities (43, 54–56). We have also shown that membrane-bound forms of sorcin co-fractionate with a subset of PS2 endoproteolytic fragments to a subcellular compartment harboring calcineurin B (Fig. 2C), another Ca\(^{2+}\)-binding molecule that appears to be involved in the regulation of both inositol 1,4,5-trisphosphate- and ryanodine-sensitive intracellular Ca\(^{2+}\) channels (57). In addition, the PS2-sorcin interaction and the translocation of sorcin to the membrane appear to be increased by elevated intracellular Ca\(^{2+}\) levels (Fig. 4). These data reveal a molecular link between PS2 and cellular Ca\(^{2+}\) channels and raise the possibility that sorcin is recruited by PS2 into a molecular complex involved in intracellular Ca\(^{2+}\) modulation. In the future, it will be important to characterize the membranous organelles harboring the PS2-sorcin complex and to determine whether the PS2-sorcin complex includes an intracellular Ca\(^{2+}\) channel (e.g. RyR) as a primary component.

Although other Ca\(^{2+}\)-binding proteins have been shown to interact with PS2, such as calnexin and calmyrin (26, 27), these interactions were demonstrated only in cells transiently transfected with PS2 cDNAs (26, 27). We (Fig. 3 and Ref. 53) and others (30) have demonstrated that overexpression of PS2 leads to an accumulation of full-length PS2, whereas levels of PS2 fragments are reduced or unchanged. Accordingly, the PS2 species that were found to interact detectably with calnexin and calmyrin were full-length PS2 but not PS2 endoproteolytic fragments (26, 27). Because growing evidence indicates that the endoproteolytic fragments comprise the functional units of the presenilins (11, 30), rather than the full-length proteins, calnexin and calmyrin most likely play a role in the proteolysis, trafficking, or stabilization of full-length PS2 intermediates. In contrast, our data show that sorcin interacts with a subset of PS2 endoproteolytic fragments but not with full-length PS2, further supporting the possibility that the sorcin-PS2 interaction has a functional role (i.e. in Ca\(^{2+}\) modulation). Implications of the sorcin-PS2 interaction for FAD remain to be elucidated. Since the large hydrophilic loop regions are divergent between PS1 and PS2 and no FAD mutation has been identified in the putative sorcin binding region of PS2 (synexin homologous domain), the exact contributions of sorcin and other PS1/PS2 loop-interacting molecules to AD neuropathogenesis have not been fully elucidated (16–19, 58). Interestingly, increased amyloid \(\beta\)-peptide levels can result from RyR-driven elevations in intracellular Ca\(^{2+}\) (59). On the other hand, decreased RyR activity correlates with early pathological changes in AD (60). To this end, we are currently investigating whether the sorcin/PS2 interaction is involved in either Ca\(^{2+}\) related increases in amyloid \(\beta\)-peptide or observed defects in

![Figure 4: Elevated intracellular calcium enhances the association of sorcin with PS2 and the recruitment of sorcin to the membrane.](http://www.jbc.org/Downloadedfrom)
RyR activity in AD. In any event, our study implies that the sorcin/PS2 interaction may play a normal and/or pathological role in intracellular Ca\textsuperscript{2+} homeostasis.

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