suREJ3, a Polycystin-1 Protein, Is Cleaved at the GPS Domain and Localizes to the Acrosomal Region of Sea Urchin Sperm*

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The sea urchin sperm acrosome reaction (AR) is a prerequisite for sperm-egg fusion. This report identifies sea urchin sperm receptor for egg jelly-3 (suREJ3) as a new member of the polycystin-1 family (the protein mutated in autosomal dominant polycystic kidney disease). suREJ3 is a multidomain, 2,681-amino acid, heavily glycosylated orphan receptor with 11 putative transmembrane segments (TMS) that localize to the plasma membrane covering the sperm acrosomal vesicle. Like the latrophilins and other members of the secretin family of G-protein-coupled receptors, suREJ3 is cleaved at the consensus GPS (G-protein-coupled receptor proteolytic site) domain. Antibodies to the extracellular 1,455-residue NH₂-terminal portion identify a band at 250 kDa that shifts in electrophoretic mobility to 180 kDa upon glycosidase digestion. Antibodies to the 1,226-residue COOH-terminal portion identify a band at 150 kDa that shifts to 140 kDa after glycosidase treatment. Antibodies to both portions of suREJ3 localize exclusively to the plasma membrane over the acrosomal vesicle. Immuno-precipitation shows that both portions of suREJ3 are associated in detergent extracts. This is the first report showing that a polycystin family member is cleaved at the GPS domain. Localization of suREJ3 to the acrosomal region provides the first suggestion for the role of a polycystin-1 protein (components of nonselective cation channels) in a specific cellular process.

Substantial progress has been made in understanding the molecular mechanisms of fertilization in both echinoderms and mammals. Upon contact with the jelly layer surrounding the egg, sea urchin sperm undergo the exocytotic acrosome reaction (AR). The AR involves Na⁺ and Ca²⁺ influx and H⁺ and K⁺ efflux. This results in increases in intracellular Ca²⁺ and pH values and elevation of cAMP and inositol triphosphate (1). In sea urchin sperm, suREJ1 was identified as a 1,450-amino acid type I transmembrane glycoprotein that is involved in the signaling cascade leading to the AR (2). suREJ1 binds to the fucose polymer of egg jelly, and the isolated polymer is capable of inducing the acrosome reaction in a manner similar to whole egg jelly (3, 4).

Sequence analysis of suREJ1 identified several extracellular domains including an epidermal growth factor domain, two carbohydrate recognition domains (CRDs), and the REJ module, a region of 1,000 amino acids that is homologous to only one other protein, polycystin-1 (2). Polycystin-1 is a multidomain glycoprotein of 4,303 amino acids with 11 putative TMS (5). The last six TMS are homologous to polycystin-2 and to voltage-activated calcium channels (6, 7). Human polycystin-2 is a 968-amino acid protein with six putative TMS (6). Mutations in the human polycystin-1 gene account for ~85% of autosomal dominant polycystic kidney disease, whereas mutations in the polycystin-2 gene account for ~15% of autosomal dominant polycystic kidney disease. This disease affects an estimated 1 in 400 to 1 in 1,000 individuals and is one of the most common hereditary disorders. All autosomal dominant polycystic kidney disease patients have renal cysts, and other manifestations include pancreatic and hepatic cysts and cardiovascular abnormalities (8, 9). Along with sequence homology to voltage-gated ion channels and transient receptor potential channels, there is accumulating functional evidence that mammalian polycystin-1 and -2 interact to form a calcium-modulated nonselective cation channel (10–12).

Several homologs of both polycystin-1 and -2 have been reported in mammals, fish, and invertebrates (7, 13, 14), demonstrating that these proteins are a new gene family whose function remains ill-defined. Recently, another human polycystin-1 homolog, hPKDREJ, has been identified. This homolog contains the ~1,000-residue REJ module plus the COOH-terminal 11 TMS of polycystin-1 (15). Most interestingly, hPKDREJ is only expressed in testis, and transcripts first appear during sperm differentiation. The homology between the sea urchin sperm suREJ proteins and mammalian hPKDREJ suggests that both animal groups may share a common signaling pathway in fertilization.

While screening a sea urchin testis cDNA library with suREJ1 probes, two new homologs were discovered, suREJ2 and suREJ3. Of these, suREJ3 is unique in that it contains all 11 TMS found in mammalian polycystin-1 (5) and hPKDREJ (15).

EXPERIMENTAL PROCEDURES

DNA Sequencing.—A suREJ1 clone isolated from a Lambda ZAP cDNA library of Strongylocentrotus purpuratus testis (2) was used for screening. Overlapping clones of suREJ3 were obtained and sequenced. After repeated rounds of screening with suREJ3 specific probes, the full-length sequence was obtained and both ends confirmed by rescreening the cDNA library.

Sequence Analysis.—suREJ3 homologs were identified using BLAST (16). Specific domains and glycosylation sites were found using the
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ProfileScan web site www.isrec.isb-sib.ch/software/PFSCAN_form.html and the PredictProtein web site dodo.cpmc.columbia.edu/predictor/predictprotein.html. The signal sequence was predicted by using the PredictProtein web site. Random jumble analysis was performed using the Biology Workbench web site PRSS program biowb. site. Site-directed mutagenesis was performed using the QuikChange kit from Stratagene, using the conditions recommended by the manufacturer.

Antibody Production—Recombinant proteins were made by amplifying DNA with exact match primers that correspond to the following amino acids: Glu32 to Lys241, SUEL; His277 to Pro2308, IH. The forward and reverse primers contained the restriction sites NdeI and BamHI. The amplified DNA was digested with restriction enzymes and ligated into the expression vector pET15b (Novagen), which contains an NdeI–BamHI fusion DNA fragment encoding a 6×His tag. The resulting R3p antibody was purified using the peptide conjugated to Affi-Gel-10 column. (Dr. Charles G. Glabe generously provided the peptide.) Cys-Phe19–Ile-Asn-Leu-Thr-His-Gly-Gln-Trp-Ser-Arg-Asp-Cys-Glu-Asn-Arg235 was used to generate the R3p antibody. The peptide was attached to maleimide-activated keyhole limpet hemocyanin (Pierce) and rabbit antibodies raised commercially (Cocalico). The resulting R3p antibody was purified by using the peptide conjugated to Sulfo-Link (Pierce).

Protein Preparation—All procedures were on ice or at 4°C. Sea urchins were spayed with injection of 0.5 μM KCl, and the undiluted sperm was collected with a Pasteur pipette. The sperm was resuspended in 0.45 μM filtered seawater (FSW). Cooelmocytes were removed by using three 5-min centrifugations at 200 × g, and sperm cells were sedimented at 5,000 × g. For isolation of sperm heads and flagella, undiluted sperm was resuspended in 20 volumes of FSW containing 50 mM Tris-HCl, pH 6.7 and 50 mM KCl to block the AR. Resuspended sperm were homogenized with a Teflon glass homogenizer to break flagella from heads. The flagella and heads were separated by differential centrifugation for 10 min (800 × g for 5 min, and sperm heads and 5,000 × g for flagella). Separation procedures were repeated until the samples were maximally enriched for heads or flagella, as determined by phase contrast microscopy. Whole sperm, heads, and flagella were resuspended in membrane solubilization buffer (0.15 M NaCl, 10 mM HEPES, 1 mM phenylmethylsulfonyl fluoride (PMSF), 2 μg/ml of leupeptin, and 1% Nonidet P-40, pH 7.4). For immunoprecipitation, 0.5% w/v of Triton X-114 was used instead of Nonidet P-40. Solubilized protein was obtained after centrifugation at 100,000 × g for 1 h (4°C). Sperm membrane vesicles were made according to the pH 9 method (23).

For wheat germ agglutinin (WGA) chromatography, solubilized sperm protein was applied to a WGA-agarose column (EY Laboratories, San Mateo, CA). The column was washed with wash buffer (0.15 M NaCl, 10 mM HEPES, 0.1% Nonidet P-40, pH 7.4), and the protein eluted in wash buffer containing 100 mM N-acetyl-d-glucosamine. SDS-PAGE was performed (24), and gels were stained with silver (25) or Coomassie Brilliant Blue.

For protein-N-glycosidase-F (PNGase-F) treatment of sperm protein, 40 μg of WGA eluate containing 0.5% SDS and 50 mM β-mercaptoethanol. Maize N. 24 μl of PNGase-F and 27.6 μl of distilled water. The sample was incubated overnight at 37°C. Following deglycosylation, the sample was separated on SDS-PAGE and transferred to PVDF. Western blots were then performed using S/C and IH antibodies.

Immunoprecipitation—2–10 μg of affinity-purified IH antibody was incubated on ice overnight with 1 mg of Triton X-114 solubilized sperm protein in a total volume of 0.5 ml. Twenty microliters of pre-washed Pansorbin (Calbiochem) was added, and the samples were rotated at 4°C for 1 h. The Pansorbin was sedimented at 12,000 × g for 1 min. Supernatants were then removed, and the Pansorbin was washed three times (5 min each) with solubilization buffer. The samples were resuspended in Laemmli sample buffer, separated on SDS-PAGE, and transferred to PVDF membranes. Membranes were probed with S/C and IH antibodies, followed by horseradish peroxidase-conjugated secondary antibody (Calbiochem). Membranes were detected with SuperSignal West Dura Extended Duration Substrate (Pierce).

Immunolocalization—Freshly spawned sperm were diluted 1:100 and incubated 10 min in FSW containing 3% paraformaldehyde and 0.1% glutaraldehyde. Fixed cells were washed three times for 10 min with phosphate-buffered saline, pH 7.4. Permeabilized sperm were incubated for 10 min in phosphate-buffered saline containing 0.2% Nonidet P-40 and were then washed three times. Non-specific sites were blocked with 3% bovine serum albumin in phosphate-buffered saline for 30 min, and then were incubated for 1 h with primary antibody in a blocking solution. This was followed by three 10-min washes, a 1-h incubation in Alexafluor 546 goat anti-rabbit IgG (Molecular Probes), and three additional washes.

RESULTS

suREJ3 Is a Multidomain Protein—The deduced amino acid sequence of suREJ3 reveals a 2,681-amino acid multidomain protein (Fig. 1). Based on Met-1 as the start site and following the 27-residue signal sequence, the presumed mature protein begins at Gly26. From the NH2 to COOH terminus, suREJ3 contains the following domains: an 84-residue sea urchin egg lectin domain (SUEL, Ref. 26), a 117-residue CRD (27), a 55-residue PKD repeat (5, 28), a 37-residue G-protein-coupled receptor proteolytic site (GPS, Ref. 29), TMS 1, a 124-poly-cystin-lipoxigenase-alpha toxin domain (PLAT, Refs. 29 and 30), TMS 2–11, and a 44-residue putative cytoskeletal component. The REJ module found in suREJ3 and polycystin-1 family members extends from Arg359 to Lys476 (Fig. 1, vertical lines; 2). The extracellular portion of the 1,485 residues preceding TMS 1 contains 23 potential N-linked glycosylation sites, and the region between TMS 1 and 11 contains eight such sites (asterisks). suREJ3 contains several domains found in polycystin-1 and hPKDREJ, as well as domains unique to suREJ3 among the polycystin family members (Fig. 2).

The SUEL domain was originally described as a galactose-binding sea urchin egg lectin (26). SUEL domains are also found in fish eggs (31, 32), and latrophilins, members of the secretin family of G-protein-coupled receptors (GPCRs, Ref. 33). The SUEL domain of suREJ3 is 44–48% similar to the SUEL domain from the mammalian latrophilins. The suREJ3 CRD is a C-type lectin domain containing the six diagnostic Cys residues (27). Its specificity for carbohydrate binding is unknown. suREJ3 contains a region of 55 amino acids that have distant homology to 16 repeat sequences present in polycystin-1, called PKD repeats. A multiple sequence alignment with the 16 repeats from human polycystin-1 and suREJ3 shows 16–26% similarity; the human PKD repeats are 20–30% similar to each other. A random jumble analysis shows that the relationship is statistically significant. suREJ3, polycystin-1, and hPKDREJ all possess a REJ module of ~1,000 amino acids of unknown function. suREJ3 contains a PLAT domain between TMS 1 and 2, which is also present in polycystin-1 and hPKDREJ. The PLAT domain is homologous to the NH2-terminal β-barrel domain of lipoxigenases (34), enzymes that peroxidize lipids (35). Of the lipoxigenases, the suREJ3 domain is most closely related to the NH2-terminal domain of mammalian 5-lipoxigenase (48% similarity). suREJ3 Is Cleaved at the GPS Domain—Prior to the first TMS is the GPS domain. This domain is present in several members of the secretin family of GPCRs, including latrophilins (33). Three members, latrophlin-1, hflamingo-1, and CD97 are known to be proteolytically processed, with cleavage between the Leu and Thr residues of latrophilin-1 (Fig. 3, Refs. 29 and 30).

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36–39). If suREJ3 was cleaved at the GPS domain, the unglycosylated NH₂ portion of 1,455 amino acids would be 160 kDa and the COOH portion would be 140 kDa. Sperm membrane proteins were solubilized in Nonidet P-40, separated by SDS-PAGE, and transferred to PVDF membrane. Immunoblots were then performed. An antibody to the S/C in the NH₂-terminal region reacted with a single component at ~250 kDa, whereas the IH antibody to the internal loop between TMS 3 and 4 reacted with a single band at ~150 kDa (Fig. 4A).

![Fig. 1. The 2,681-deduced amino acid sequence of suREJ3.](http://www.jbc.org/)

Fig. 1. The 2,681-deduced amino acid sequence of suREJ3. Domains are highlighted in gray, with the exception of the REJ module, which is denoted by arrows in the sequence. Names of domains appear at the beginning of the sequence. The putative cleavage site within the GPS domain (Leu 1455) is labeled with an arrow. The underlined SUEL/CRD region denotes the bacterially expressed antigen for the S/C antibody. The CRD line above 17 residues of the CRD shows the synthesized peptide antigen used for the R3p antibody. The underline between TMS 3 and 4 indicates the bacterially expressed antigen for the IH antibody. Asterisks (*) above the sequence indicate the N-linked glycosylation sites. Arrows (vvv) above the sequence indicate two protein kinase A sites, both in the cytoplasmic loops. Putative transmembrane segments (TMS1-11) are bold in italics and labeled above the sequence. The GenBank® accession number is AF422153.
trophoretic mobility shifts of the S/C-reacting band to 180 kDa and the IH-reacting band to 140 kDa (Fig. 4B). The most likely explanation for these results is that, like the GPCRs, suREJ3 is cleaved into approximately equal halves at the GPS domain, the NH2-terminal portion being heavily glycosylated. Association of the two halves of suREJ3 with each other was confirmed by immunoprecipitation of both proteins from Zwittergent 3-10 extracts of sperm using the IH antibody (Fig. 5).

Like suREJ1, the NH2 terminus of suREJ3 can be partially removed from the membrane by incubating sperm in pH 9.2 FSW (23), whereas the COOH terminus is exclusively associated with the membrane fraction (Fig. 7). This indicates that the interaction between the NH2 and COOH termini is not because of disulfide bonds, but rather because the interaction is noncovalent.

**DISCUSSION**

The extracellular portion of suREJ3 contains three domains: SUEL, CRD, and the PKD repeat, all of which indicate a role in extracellular matrix interactions. The SUEL domain and CRD suggest a lectin-like interaction with carbohydrates, presumably from the multicomponent egg extracellular matrix known as egg jelly (3). We do not know the identity of possible ligands binding these three domains. The SUEL domain was first identified as an α-D-galactose-specific lectin in eggs of the sea urchin *A. crassispina* (26). SUEL is a 105-amino acid protein that forms a homodimer that localizes to the egg cortex after fertilization. SUEL binding is calcium-independent and does not

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**Fig. 2.** The domain structure of suREJ3, suREJ1, polycystin-1 and -2. The key defines each domain. TMS are numbered above suREJ3, suREJ1, polycystin-1, and PKDREJ are homologous to polycystin-2 in the region with the last 6 TMS.

**Fig. 3.** Alignments of GPS domains. Dashes are included for alignment. Black boxes denote identity and gray boxes similarity. The arrow above the alignment indicates the GPS cleavage site. The GenBank accessions numbers are as follows: suREJ3 (AF422153), human polycystin-1 (P98161), hPKDREJ (XP_010050), latrophilin-1 (T14324), human Flamingo-1 (AAG00080), and human CD97 (AAB36682).

**Fig. 4.** Immunoblots with suREJ3 antibodies. A, immunoblot of Nonidet P-40 solubilized total sperm protein identifying the NH2 terminus (S/C) and COOH terminus (IH) of suREJ3. The relative molecular masses are shown on the right. B, immunoblots with S/C and IH antibodies after PNGase-F digestion of WGA eluate of Nonidet P-40 solubilized sperm protein (+, with enzyme; −, no enzyme). Five micrograms of protein were loaded per lane.

**Fig. 5.** Both halves of suREJ3 remain associated in detergent extracts of sperm heads. IH antibody (+) was used for immunoprecipitation with 2 mg of Zwittergent 3-10 solubilized protein from isolated sperm heads. The washed Pansorbin containing the attached antibody/antigen complex was boiled in Laemmli sample buffer. The supernatant was separated by SDS-PAGE, and transferred to PVDF membrane. The blots were probed with either the S/C or IH antibodies. Control immunoprecipitates with no IH antibody (−) did not bind either half of suREJ3.
require reduction. The mammalian orphan GPCRs, known as latrophilins, also contain SUEL domains. Latrophilin-1 binds α-latrotoxin (black widow spider toxin) in a calcium-independent manner, resulting in massive exocytotic release of neurotransmitter (40). Comparison of rat and bovine latrophilins shows that the SUEL domain is the most conserved part of the protein, suggesting that it is important in latrophilin signaling (41). Although G-protein subunits have been found in sea urchin spermatozoa, there is no evidence that they are involved in triggering the AR (42).

The single CRD of suREJ3 has the diagnostic structure of a calcium-dependent lectin (27). suREJ1 has two NH₂-terminal-located CRDs, which are only 50% identical to each other over an alignment of 120 residues (21). The single CRD of suREJ3 is 52% identical to CRD-1 of suREJ1 and 47% identical to the suREJ1 CRD-2. The sequences of these CRDs do not disclose their sugar binding specificity. suREJ3 has only one PKD repeat, whereas human polycystin-1 has 16. PKD repeats are not found in Lov-1, the Caenorhabditis elegans homolog of polycystin-1 (13, 14). The most likely explanation is that duplication of PKD repeats occurred in the evolution of the vertebrates on the way to mammals. NMR studies show the PKD repeat has a β-sandwich fold, similar to the immunoglobulin fold, but it is evolutionarily unrelated to IgG molecules (28). The PKD repeats from polycystin-1 mediate both cis- (on the same cell) and trans- (cell-to-cell) calcium-dependent, homotypic interactions (43). The aforementioned data suggest that the single PKD repeat of suREJ3 could act in homotypic clustering of the protein in the acrosomal region.

The REJ module was originally described as a domain of 707 amino acids found in suREJ1 and human polycystin-1 (2). The addition of other polycystin-1 homologs to the data base showed that the REJ module was ~1,000 amino acids (7). This domain also occurs in the mammalian testis-specific PKDREJ. The GPS cleavage site is within this domain in suREJ3. The REJ module is not found in the secretin family of GPCRs, which have the GPS domain; therefore, possession of the REJ module is independent of possession of a GPS site. Because the GPS site is known to be extracellular, and PLAT is exclusively intracellular, the positions of these two domains support the topology presented herein for the TMS of suREJ3. Also, the IH antibody to the putative intracellular sequence between TMS 3 and 4 binds only to the acrosomal regions in sperm that have been detergent permeabilized.

Among the secretin family of GPCRs, latrophilins are unique in their relationship to suREJ3, because they contain both the SUEL and GPS domains. This report demonstrates that suREJ3 is cleaved and that the deglycosylated halves correspond to their predicted sizes based on cleavage at the GPS domain. Although we do not experimentally show the exact point of cleavage of suREJ3, based on work with other GPS-containing proteins, we believe that suREJ3 is cleaved at the consensus Leu-Thr site (Fig. 2). This is the first evidence that a polycystin-1-like protein is cleaved. The presence of this domain in suREJ1 may also explain the previous observation that 70% of suREJ1 can be removed from sperm by treatment with pH 9.2 seawater for 5 h (2). Whether mammalian polycystin-1 and hPKDREJ are also cleaved at the GPS domain remains to be demonstrated. The two halves of suREJ3, although associated in detergent extracts of sperm membranes (Fig. 5), are not as tenaciously associated as are the two halves of latrophilin-1. Unlike latrophilin-1, the two halves of suREJ3 dissociate in SDS-mercaptoethanol sample buffer without the addition of 8 M urea (39). Also, like suREJ1, the NH₂-terminal half of suREJ3 can be partially removed from sperm by treatment with pH 9.2 seawater, showing that it is a peripheral component of the cell membrane. The relationship between suREJ3 and latrophilins and the location of suREJ3 over the acrosomal vesicle suggests that suREJ3 may regulate AR exocytosis. α-Latrotoxin does not induce the AR of sea urchin sperm (data not shown). This is not surprising, because black widow spider toxins show phylogenetic specificity (44). Also, recent work suggests that α-latrotoxin does not activate latrophilin-1 to cause exocytosis, but instead functions by tethering to latrophilin-1 and inserting itself into the membrane to form pores (45).

In addition to the location of suREJ1 and suREJ3 on the cell membrane covering the acrosomal vesicle, the exocytosis reg-
ular proteins, soluble NSF attachment protein (SNAP)-25, vesicle-associated membrane protein (VAMP), and syntaxin are all exclusive to the acrosomal region of sea urchin sperm (46, 47). Antibodies to suREJ1 induce the exocytotic AR of sea urchin sperm (2). However, neither the S/C and R3p antibodies made to the extracellular NH2-terminal half, nor the III antibody made to the intracellular COOH-terminal half of suREJ3 induce the AR. suREJ3 is known to bind to the fusocose sulfatel polymer of egg jelly (2, 3). Two different isoforms of this polymer exist that differ in the placement of sulfate groups. Both are linear polymers of α-1,3-linked fusose with a molecular mass of approximately one million (4). We do not know if the fusocose sulfatel polymer, or other ligands in egg jelly, bind to suREJ3. The AR always requires the fusocose sulfatel polymer; however, oligosaccharide chains of egg jelly glycoproteins greatly enhance the fusocose sulfatel polymer-induced AR, suggesting that other sperm receptor proteins are involved in the inductive mechanism (48). Many scenarios are possible for the involvement of both suREJ1 and suREJ3 in the AR. They may represent redundant signaling pathways, or the two sea urchin sperm receptors could interact in the same pathway.

From the similarities of the proteins shown in Fig. 2, and the fact that polycystin-1 and -2 (11), polycystin-2L (10), and polycystin-2 from syncytiotrophoblast (12) form nonsel ective cation channels, it is valid to speculate that suREJ3 may form an ion channel or be a component of the regulatory apparatus of a channel. Both polycystin-2 and transient receptor potential channels (TRPCs) are excellent candidates for components of such a channel in the sperm AR. TRPCs were first described in Drosophila photoreception as store-operated cation channels (49). TRPC-1, a mammalian TRP homolog, associates with polycystin-2 through the COOH-terminal coiled-coil domain and also TMS regions (50). Mouse TRPC-2 has been shown to mediate the sustained increase in calcium associated with the sperm AR (51).

Unlike polycystin-1 and -2 (50, 52), sea urchin suREJ3, mammalian PKDREJ (15) and C. elegans Lov-1 (13) do not have a predicted coiled-coil domain in their COOH-terminal ends. Thus, these three proteins, which are all involved in male reproduction, might interact with proteins through other domains. Although clearly related to each other in their COOH-terminal halves, there is much less relationship among them in their NH2-terminal halves. Until the discovery of the sea urchin REJ proteins, the proteins associated with gamete recognition in sea urchins have been unrelated to known mammalian proteins. The smaller genomic size of the sea urchin (800 megabases) and the characteristic of fewer duplicated genes than found in mammals may make the sea urchin a more tractable model for discovering the pathways of signal transduction leading to the deuterostome sperm AR. Further study of suREJ3 may help clarify the function of polycystin-1 and its role in the genesis of polycystic kidney disease in humans, as well as contribute to the understanding of the molecular mechanisms of sperm-egg interactions in both sea urchins and mammals.

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