Tight Junction Protein Par6 Interacts with an Evolutionarily Conserved Region in the Amino Terminus of PALS1/Stardust

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Tight junctions are the structures in mammalian epithelial cells that separate the apical and basolateral membranes and may also be important in the establishment of cell polarity. Two evolutionarily conserved multiprotein complexes, Crumbs-PALS1 (Stardust)-PATJ and Cdc42-Par6-Par3-atypical protein kinase C, have been implicated in the assembly of tight junctions and in polarization of Drosophila melanogaster epithelia. These two complexes have been linked physically and functionally by an interaction between PALS1 and Par6. Here we identify an evolutionarily conserved region in the amino terminus of PALS1 as the Par6 binding site and identify valine and aspartic acid residues in this region as essential for interacting with the PDZ domain of Par6. We have also characterized, in more detail, the amino terminus of Drosophila Stardust and demonstrate that the interaction mechanism between Stardust and Drosophila Par6 is evolutionarily conserved. Par6 interferes with PATJ in binding PALS1, and these two interactions do not appear to function synergistically. Taken together, these results define the molecular mechanisms linking two conserved polarity complexes.

Epithelial cells possess asymmetry with respect to the apicobasal axis reflected by the differential distribution of proteins and lipids in the apical and basolateral surfaces (1). Polarized mammalian epithelial cells have a tight junctional seal, which serves as a physical barrier that separates apical and basolateral membranes. It has been shown that proteins containing the PDZ (postsynaptic density-95/discs large/ZO-1) domain play an important role during cell polarization (2), and multiple PDZ protein complexes are involved in the assembly and maintenance of tight junctions.

One of the major groups of PDZ proteins is the membrane-associated guanylate kinase protein, which has one or more PDZ domains as well as an Src homology 3 domain and a noncatalytic guanylate kinase domain. Genetic and biochemical studies in Drosophila melanogaster have shown that membrane-associated guanylate kinase protein Stardust (Sdt) interacts with the transmembrane protein Crumbs (Crb) through its PDZ domain, and mutations in either Crb or Sdt cause polarity defects in Drosophila epithelia (3). The mammalian homologue of Sdt is PALS1 (protein associated with Lin seven) (4). Like Sdt, the PDZ domain of PALS1 binds the C-terminal tail of mammalian Crb isoforms, and PALS1 also interacts with a multi-PDZ domain protein, PATJ (PALS1-associated tight junction protein), through L27 (Lin-2 and Lin-7) domain dimerization (4, 5). The Crb-PALS1-PATJ complex localizes to the tight junctions of mammalian epithelial cells, and the disruption of the complex leads to defects in cell polarity (6). Similarly, the Drosophila PATJ homologue, formerly known as discs lost (Dlt) (7, 8), can interact with the L27 domain of Sdt. Therefore, the analogous complex in D. melanogaster is Crb-Sdt-PATJ.

Another evolutionarily conserved tight junction complex is composed of PDZ proteins Par3, Par6, and aPKC and the GTP-loaded form of the small GTPase Cdc42 (9–12). The Par3-Par6-aPKC complex is important for determining polarity in many cell types, including D. melanogaster neuroblasts, the Caenorhabditis elegans zygote, and mammalian epithelial cells (12–14). aPKC-α and -ζ interacts with Par6 through PB1 (Phox and Bem 1) domain dimerization in the amino terminus of both proteins (11, 12, 15, 16), and both aPKC and Par6 can bind Par3 (11). Par6 also interacts with the active form of Cdc42 and Rac. Both its Cdc42/Rac-interactive binding domain (CRIB)-like motif and the adjacent PDZ domain are required for this interaction (11, 12, 17). The Drosophila homologues of Par3, Par6, and aPKC are Bazooka, DmPar6, and DaPKC, respectively. They also form a complex and localize at the subapical region of the Drosophila epithelia (18).

The two tight junction complexes have been studied separately until recently, when they were connected by the interaction between PALS1 and Par6 (19). It was shown that PALS1 and Par6 bind directly, and the interaction is between the PALS1 amino terminus and the CRIB and PDZ domains of Par6. PDZ domains usually recognize the extreme carboxyl terminus of binding partners, but they can also recognize an internal binding site if the site is presented in a β-finger structure that mimics the protein carboxyl terminus (2). In this study, we further characterized the PALS1-Par6 interaction. We found that the Par6 binding site in the PALS1 amino terminus and the interaction mechanism are conserved in the Sdt-DmPar6 interaction in D. melanogaster. We also studied the relationship between PALS1-PATJ interaction and PALS1-Par6 interaction, and our results indicate that the binding may be competitive rather than synergistic.

EXPERIMENTAL PROCEDURES

Antibodies—Mouse monoclonal anti-Myc (9E10, Santa Cruz Biotechnology, Inc., Santa Cruz, CA), and rabbit polyclonal anti-HA (Y11; Upstate Biotechnology, Inc.) antibodies were utilized for immunoprecipitation and Western blotting experiments. Mouse anti-GST1 anti-
Par6 Binding Site in PALS1

**A**

**B**

**C**

**Fig. 1.** PALS1 NH2-terminal ECR1 mediates Par6 binding. **A**, schematic illustration of the domain structure of PALS1 and Par6. **B**, alignment of the NH2-terminal conserved regions in *Drosophila* (*Dm*), zebrafish (*Dr*), mouse (*Mm*), and human (*Hs*) PALS1. Two conserved regions were found and named ECR1 and ECR2 (for evolutionarily conserved regions 1 and 2). Deletion of ECR1 prevents pull-down of HA-Par6. **C**, deletion of ECR1 or ECR2 deleted was immobilized on agarose beads and incubated with cell extract from HEK293 cells transiently transfected with HA-Par6 or Myc-PATJ. Precipitating proteins were detected by immunoblotting for HA-Par6 or Myc-PATJ. Cell lysates were also immunoblotted to monitor protein expression levels. GUK, guanylate kinase domain.

**DNA Constructs**—HA-Par6B, Myc-PALS1, GST-PALS1(1–181), and Myc-PATJ constructs were generated as previously described (4, 19). GST-PALS1(1–181) DNA constructs together with 0.5 μg of pRK5-Myc-PALS1 V37G or pHA3-Par6B DNA constructs were used to create recombinant GST fusion proteins consisting of the U1 region and L27N domain of PALS1 and Par6. A schematic of the domain structure of PALS1 and Par6 is shown in Fig. 1A. **Cell Culture**—MDCK type II cells and HEK293 cells were grown in Dulbecco’s modified Eagle’s medium (Invitrogen) containing 100 units of penicillin, 100 μg/ml streptomycin sulfate, 2 mM l-glutamine, and 10% fetal bovine serum. MDCK Myc-PALS1 (wild type and V37G mutant) and HA-Par6B cell lines were maintained in media supplemented with 600 μg/ml G418 and 300 μg/ml hygromycin B, respectively.

**DNA Constructs**—Early passage MDCK cells grown to ~30% confluence on 10-cm plastic dishes were transfected with 5 μg of pRK5-Myc-PALS1 V37G or pHA3-Par6B DNA constructs together with 0.5 μg of pSV2neo (for G418 selection) or pTRE2hyg (for hygromycin B selection) empty vectors using Fugene6 reagent (Roche Applied Science). Transfected cells were replated in medium containing 800 μg/ml G418 or 600 μg/ml hygromycin B 48 h after transfection. Medium was changed every 2–3 days. After 12 days of selection, surviving clones were picked and screened for Myc-PALS1 V37G or HA-Par6B expression by immunostaining and Western blot.

**Immunoprecipitation and Blotting**—Plasmids (3 μg for GST pull-down and 2 μg for communoprecipitation or as indicated in the experiment) were transfected with Fugene6 reagent into HEK293 cells grown to 50% confluence on 10-cm dishes. After 48 h, cells were collected in 0.5 ml of lysis buffer (50 mM Tris (pH 7.4), 150 mM NaCl, 10% glycerol, 1 mM Triton X-100, 1.5 mM MgCl2, 1 mM EGTA, 10 mM Na4P2O7, 1 mM Na3VO5, 1 mM phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin, and 20 μg/ml aproline). HA-Par6 stable MDCK cells were grown to confluence on 10-cm dishes and collected in 0.5 ml of lysis buffer likewise. Lysates were cleared by centrifugation (12,000 × g for 15 min at 4 °C). For GST-PALS1 pull-downs, 10 μg of GST protein was used per experiment. Immunoprecipitation and Western blotting was performed as previously described (19).

**Immunofluorescence Microscopy and Imaging**—MDCK cells were seeded at a high density into the Lab-Tek II chamber slide system (Nalge Nunc). They were fixed in 4% formaldehyde/PBS for 10 min, permeabilized in 1% SDS/PBS for 5 min, and blocked in 2% goat serum/PBS for 1 h. Chamber slides were incubated with primary antibodies in blocking solution (monoclonal anti-Myc 9E10 (1:1000), monoclonal anti-ZO-1 (1:400), monoclonal anti-E-cadherin (1:1600), and polyclonal anti-PALS1 (1:200) overnight in a humidified chamber at 30 °C. After extensive washes with PBS, chamber slides were incubated with fluorochrome-conjugated secondary antibody (1:1500 in blocking solution) for 2 h at 30 °C. Subsequently, chamber slides were washed three times with PBS and mounted with ProLong antifade reagent (Molecular Probes, Inc., Eugene, OR). Immunofluores-
cence microscopy was performed at the University of Michigan Diabetes Center with an Olympus FluoView 500 scanning laser confocal microscope.

RESULTS

PALS1 Interacts with Par6 through an Evolutionarily Conserved Region in Its Amino Terminus—It was previously shown that PALS1 interacts with Par6 through its amino-terminal region aa 1–181 (19), which consists of the U1 region (aa 1–120) and the L27N domain (aa 121–181) (Fig. 1A). The L27N domain mediates the PALS1-PATJ interaction by L27 domain heterodimerization with the L27 domain of PATJ, whereas the function of the PALS1 U1 region is largely unknown. We made further deletions in the PALS1 amino terminus and performed GST pull-down experiments to precipitate HA-Par6 expressed in HEK293 cells. We found that the first 20 amino acids of the U1 region are not required in this interaction, whereas the first 20 amino acids of the L27N domain are essential (data not shown). Thus, we determined the minimum binding region in PALS1 required for Par6 binding to be amino acids 21–140.

We performed an alignment of the PALS1 amino terminus and found two regions conserved in PALS1 from human, mouse, zebrafish, and Drosophila PALS1 homologue, Stardust (Fig. 1B). We named these regions evolutionarily conserved region 1 and 2 (ECR1 and ECR2, respectively). A GST-PALS1 (1–181) fusion protein with the ECR1 deleted cannot bind HA-Par6, whereas binding to Myc-PATJ is not affected (Fig. 1C). In contrast, deletion of the ECR2 region has no effect on Par6 binding. We also expressed the ECR1 peptide alone fused to GST, but this was not able to bind Par6. This indicates that the ECR1 region of PALS1 is necessary but not sufficient for Par6 binding.

Point Mutations in the PALS1 ECR1 Reduce Interactions with Par6—To further characterize the Par6 binding site, we mutated each amino acid in the PALS1 ECR1. Hydrophobic residues were mutated to glycine, whereas the other residues were mutated to alanine. GST-PALS1(1–181) containing ECR1 point mutations were bound to glutathione-agarose beads, and their ability to precipitate HA-Par6 was tested. Two mutations, V37G and D38A, severely reduced the binding of Par6 (Fig. 2A). In contrast, point mutations in the PALS1 L27N domain, V150G and L154G, that abolish the interaction with PATJ had no effect on Par6 interactions. We next made more conservative mutations in Val-37 and Asp-38 by generating V37I and D38E and found near wild type binding of these two mutants to Par6 (Fig. 2A, bottom right panel). Similar experiments were also carried out in MDCK cells stably expressing HA-Par6. The GST-PALS1(1–181) containing ECR1 point mutations bound to glutathione-agarose beads, and their ability to precipitate HA-Par6 was tested. Two mutations, V37G and D38A, severely reduced the binding of Par6 (Fig. 2A). In contrast, point mutations in the PALS1 L27N domain, V150G and L154G, that abolish the interaction with PATJ had no effect on Par6 interactions. We next made more conservative mutations in Val-37 and Asp-38 by generating V37I and D38E and found near wild type binding of these two mutants to Par6 (Fig. 2A, bottom right panel).

Simlar experiments were also carried out in MDCK cells stably expressing HA-Par6. The GST-PALS1(1–181) V37G and D38A bound HA-Par6 poorly, whereas the V37I mutant and the D38E mutant had no significant effect on binding (Fig. 2B). Point mutations in the PALS1 L27N domain did not affect the interaction between PALS1 and Par6.

Par6 Binding Site in Drosophila Stardust—We examined whether this Par6 binding site was functional in the PALS1 Drosophila homologue, Stardust. According to the published sequence (21, 22), Stardust has only one L27 domain and a much larger U1 region at its amino terminus when compared...
with PALS1 homologues from other species. In this large Stardust U1 region, there is one perfectly matched ECR1 and another region that is an imperfect match for an ECR1 region. There are also two ECR2 motifs. We designed a 5' primer against the ECR1 and a 3' primer against a conserved region in the PDZ domain and performed a PCR from Drosophila embryonic cDNA (0.5-12 h pooled). A PCR product of 1.2-kb was obtained and the sequencing of this product reveals a much shorter U1 region of 256 aa. A 1299-bp fragment described in Stardust was missing from our PCR product, and this fragment is predicted to be an exon in the Drosophila genome data base (FlyBase, available on the World Wide Web at flybase.bio.indiana.edu). Using additional oligonucleotides from this region, we were unable to obtain a product containing this exon in any of our PCRs. Thus, we believe the predominant form of Stardust mRNA found in the embryo is the one shown in Fig. 3A.

This U1 region (aa 1-256) of Drosophila Stardust was cloned and fused to GST. GST-Sdt(1-256) can bind HA-Par6 in a similar fashion to GST-PALS1(1-181), but it does not interact with PALS1 because it does not contain an L27 domain (Fig. 3B). Val-19 and Asp-20 in Stardust ECR1 are also critical for its binding with Par6. A GST pull-down experiment was carried out as above, with the GST-PALS1(1-181), GST-Sdt(1-256), or the GST-Sdt(1-256) with Val-19 and Asp-20 in its ECR1 mutated to Gly and Ala, respectively, incubated with HEK293 cells transiently transfected with HA-Par6 or HA-DmPar6, the Drosophila homologue of Par6. The V19G and the D20A mutants also show a decrease in the ability to bind both mammalian Par6 and Drosophila Par6.

Interaction between the PALS1 ECR1 and Par6 CRIB-PDZ Domains—Previous results also showed that the PALS1-Par6 interaction is mediated by a region that covers both the semi-CRIB domain and the PDZ domain in Par6 (19). Since the Par6 semi-CRIB domain and PDZ domain can form an integral structure and interact with Cdc42 (23), we wanted to test whether the Par6 semi-CRIB domain and PDZ domain also work coordinately to bind PALS1 or whether either one of them is sufficient for the interaction. Different Par6 deletion mutations were made and co-transfected into HEK293 cells with wild type Myc-PALS1 (Fig. 4A). Mutants with either the CRIB domain alone or PDZ domain alone cannot co-immunoprecipitate with Myc-PALS1, whereas the mutant with both domains present can interact with PALS1, although the interaction is not as strong as that of Par6 wild type (Fig. 4B).

The V37A mutation was generated in full-length PALS1, and the mutant showed decreased interaction with Par6 wild type in a coimmunoprecipitation experiment. A Par6 point mutation, M235W, also resulted in weakened interactions with PALS1 wild type in a coimmunoprecipitation (Fig. 4B). Par6 M235W alters a methionine residue in the PDZ binding pocket into a bulky tryptophan to block the PDZ domain-binding pocket, and this mutation abolishes the interaction between Par6 and the two mammalian lethal giant larvae isoforms (mLgl-1 and mLgl-2) (24).

We noted that PALS1 V37G did not completely abolish binding with Par6, as was seen with GST-PALS1(1-181) V37G, so it is possible that there are other Par6 binding sites in PALS1 outside the aa 1-181 region. Also, we wanted to investigate the relationship between the PALS1 ECR1 and Par6 PDZ domain, so we co-transfected different PALS1 truncation mutants (Fig. 4A) with either Par6 wild type or Par6 M235W mutant and performed coimmunoprecipitation experiments. PALS1(1-181) shows a dramatic decrease in binding to Par6 M235W like full-length PALS1, whereas the PALS1 ΔN only has residual interaction with both Par6 wild type and Par6 M235W. These coimmunoprecipitation results, together with the GST pull-down results in Fig. 2, suggest that the PALS1-Par6 interaction is through PALS1(1-181) and Par6 CRIB-PDZ domains, and the interaction between PALS1 ECR1 (the valine residue) and Par6 PDZ binding pocket is a major contributor to the binding between PALS1 and Par6.
PALS1 V37G Mutant Is Localized to the Tight Junction—To determine the subcellular localization of the PALS1 V37G mutant, a MDCK cell line that stably expresses Myc-PALS1 V37G was generated. As shown in Fig. 5, Myc-PALS1 V37G mutant is localized at the tight junction as detected by Myc and PALS1 staining. It was co-localized with the tight junction marker ZO-1 and is above the adherens junction marker E-cadherin in the Z-section image (data not shown) just as the endogenous PALS1 did in the wild type MDCK cell line (4). It was previously shown that the L27N domain of PALS1 is responsible for tight junction targeting, and deletion of just the U1 region did not disrupt the localization of PALS1 (4). The V37G mutation in PALS1 U1 region does not affect the PALS1-PATJ interaction, and this probably explains the normal localization of this mutant in epithelial cells.

Par6 Interferes with PATJ in Binding PALS1—A region of the PALS1 L27N domain is required for binding Par6, but the reason for this requirement is not clear. However, as shown in Fig. 2A, mutations in PALS1 L27N domain that abolish PALS1-PATJ binding do not affect the PALS1-Par6 binding; thus, we wanted to determine whether PALS1 and PATJ work synergistically to bind Par6 as seems to be suggested by studies in Drosophila (25). A constant amount of Myc-PATJ and increasing amounts of HA-Par6 were co-transfected into HEK293 cells, and the cell lysates were incubated with GST-PALS1(1–181)-agarose beads. With the increase of Par6 expression, there is an increase in Par6 binding to GST-PALS1(1–181) and a decrease in PATJ binding (Fig. 6). This result suggests that Par6-PALS1 binding can interfere with PATJ-PALS1 binding, and these two interactions do not work synergistically.
DISCUSSION

In this report, we identified the Par6 binding site in the PALS1 amino-terminal region and showed that the same binding site also exists in Stardust, the Drosophila PALS1 homologue. The PALS1-Par6 binding is mainly mediated by the interaction between the binding site in the PALS1 ECR1 and the Par6 PDZ domain binding pocket. PDZ domains are intracellular modules that usually bind the extreme carboxyl terminus of a protein and also can recognize internal sites when that site is presented in a β-finger structure that mimics the protein carboxyl terminus (2). The β-finger structure is usually stabilized by disulfide bonds or salt bridges. In the case of neuronal nitric-oxide synthase (nNOS)-syntrophin interaction, an Arg residue 9 aa downstream of the 0-position of the internal binding site in neuronal nitric-oxide synthase forms a salt bridge with the Asp residue and stabilizes the β-finger structure (26).

We also found an Arg residue 9 aa downstream of Val-37 in PALS1 that is conserved among species, but the mutation of this Arg to Asp did not interfere with its binding to Par6 in GST pull-down experiments (data not shown).

A recent report has shown that Drosophila Par6 and PATJ bind to each other directly and that the interaction is between the amino terminus of DmPar6 and the third PDZ domain of Dm-PATJ (25). We cotransfected HEK293 cells with mammalian Par6 and PATJ, and we did not see the coimmunoprecipitation of the two proteins. However, we do not exclude the possibility of Par6-PATJ interaction in the process of polarization of MDCK cells, and this interaction may bring new complexity to the dynamic cooperation of the two tight junction complexes.

The newly identified mLgl-Par6 interaction shows similarities to the PALS1-Par6 interaction. It is mediated by binding of the amino-terminal region of mLgl, which contains several WD40 repeats, to the Par6 PDZ domain (24, 27, 28), and the Par6 M235W mutant cannot bind mLgl-1 or mLgl-2 (24). There is no detectable sequence homology between the mLgl amino terminus and PALS1 amino terminus, and there is no sequence similar to the PALS1 ECR1 found in mLgl. However, the similarities of the two interactions suggest that further study of the mLgl-Par6 interaction will probably help to elucidate the mechanism of the PALS1-Par6 interaction and vice versa.

There was a requirement for the PALS1 L27N domain in the interaction between Par6 and PALS1, yet its role is still not clear, since the Drosophila Stardust amino terminus lacking the L27 domain could still bind Par6 (Fig. 3B). We made a series of deletions in the Stardust U1 region and found that Sdt(1–194) bound Par6 as strongly as Sdt(1–256), and Sdt (1–154) still had substantial binding to Par6. Based on these findings, we speculate that the first 20 amino acids of the PALS1 L27N domain help the PALS1 U1 region fold into a proper structure when the protein is expressed as a GST fusion protein. Similarly, we would speculate that this L27 region is not required in Stardust because of the larger amino terminus that can fill this role. Previous circular dichroism study suggested that L27 domains are largely unfolded individually, but when associated with their heterodimerization partners they show a significant increase in helicity as well as a cooperative unfolding transition with increasing temperature (29). We propose that PALS1 may have two conformational states in its amino terminus. In state 1, when PALS1 interacts with PATJ, the PALS1 L27N domain is fully folded, heterodimerizing with the PATJ L27 domain. In state 2, the PALS1 L27N domain is largely unfolded, and the first 20 amino acids of the L27N domain fold with the adjacent U1 region to form a structure to present the Par6 binding site in ECR1 to the Par6 PDZ domain. However, it is possible that the Par6 binding site is also properly presented when the PALS1 L27N domain is fully folded, but in this case PATJ binding and Par6 binding may interfere with each other due to steric hindrance.

The fact that Stardust lacks the L27N domain but still can bind Par6 also suggests that PATJ does not promote the PALS1-Par6 interaction by forming a protein complex with the two, and since the PALS1 L27N domain is shared between the two interactions, it is reasonable to think that PALS1 does not interact with Par6 and PATJ at the same time. However, these studies were performed in HEK293 cells, and it is possible that such cooperative interactions may occur during polarization in MDCK cells. The true nature of these interactions will require additional studies, in particular structural analysis. Recently, Prehoda and co-workers (30) studied the structure of the PDZ domain of Drosophila Par6 bound to a carboxyl-terminal peptide ligand in the absence of Cdc42. A mutagenesis study of this carboxyl-terminal ligand suggested that the P0 residue and the P–1 residue are essential for the recognition of Par6 PDZ domain, whereas the P–2 residue was not important. This is in contrast to classic PDZ domain peptide interactions, where the P0 residue and the P–1 residue are essential. This could help explain why we found two adjacent residues in the PALS1 ECR1 that are important for Par6 interaction. Some of their data also supported the idea that the PALS1-Par6 interaction is mediated by the PDZ binding pocket of Par6. Overall, our studies indicate that the ECR1 region in PALS1 is essential for the interaction between the Par6 CRIB-PDZ region and PALS1. Our data also show an important role for the remainder of the U1 region, suggesting that the U1 region possibly folds into a specific tertiary structure to present the ECR1 motif to Par6. Structural studies will be necessary to confirm this speculation.
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