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The planar cell polarity effector protein Wdpcp (Fritz) controls epithelial cell cortex dynamics via septins and actomyosin

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ABSTRACT

Planar cell polarity (PCP) signaling controls polarized behaviors in diverse tissues, including the collective cell movements of gastrulation and the planar polarized beating of motile cilia. A major question in PCP signaling concerns the mechanisms linking this signaling cascade with more general cytoskeletal elements to drive polarized behavior. Previously, we reported that the PCP effector protein Wdpcp (formerly known as Fritz) interacts with septins and is critical for collective cell migration and cilia formation. Here, we report that Wdpcp is broadly involved in maintaining cortical tension in epithelial cells. *In vivo* 3D time-lapse imaging revealed that Wdpcp is necessary for basolateral plasma membrane stability in epithelial tissues, and we further show that Wdpcp controls cortical septin localization to maintain cortical rigidity in mucociliary epithelial cells. Finally, we show that Wdpcp acts via actomyosin to maintain balanced cortical tension in the epithelium. These data suggest that, in addition to its role in controlling plasma membrane dynamics in collective mesenchymal cell movements, Wdpcp is also essential for normal cell cortex stability during epithelial homeostasis.

1. Introduction

The planar cell polarity (PCP) pathway is a critical regulator of polarized cell behaviors [1]. Studies into the molecular basis of PCP signaling have focused predominantly on the question of how these proteins become asymmetrically localized in cells (i.e. how the cell makes the decision to become polarized) [2], while much less is known about how cells act on PCP-mediated polarization decisions (i.e. how the PCP components interface with fundamental machinery of cell behavior such as the cytoskeleton), especially in vertebrates [3]. Some insights have come from studies of the *Drosophila* "PCP effector" (PPE) proteins, including Inturned, Fuzzy and Fritz. These novel proteins are essential for planar cell polarity in the fly wing, and appear to act genetically downstream of the core PCP proteins [4–9]. Curiously, recent data suggest that the three *Drosophila* PPE effector proteins form a physical and functional complex, though Fritz also appears to play additional roles independent of this complex [10]. Indeed, Fritz is essential for the planar organization of *Drosophila* embryonic denticles, but neither the core PCP proteins nor the Fuzzy or Inturned are required in this setting [7]. These data suggest that Fritz controls as yet undefined cell biological processes that are acted upon by multiple inputs, including the core PCP proteins. Thus understanding exactly how Fritz interacts with the cell biological machinery of polarization (i.e. the cytoskeleton, vesicle trafficking, etc.) is an important and unresolved issue.

Previously, we discovered that the vertebrate homologue of *Drosophila* Fritz, Wdpcp is also necessary for polarized cell migration during collective cell movements of mesenchymal cells during gastrulation [11]. In that context, we found that Wdpcp localizes to the cell cortex where it is required for cortical localization of septins [11]. Septins are highly conserved GTP bound proteins which form filamentous cytoskeleton by hetero-oligomerization [12]. It is known that the major function of septins is compartmentalizing the plasma membrane by forming a rigid diffusion barrier among different membrane compartment such as the cleavage furrow, the neck of ciliary membrane and the annulus of sperm [13]. Indeed, septin-based compartmentalization of cortical actomyosin is essential both for cytokinesis in animal cells [14] and for PCP-mediated collective behavior of mesenchymal cells during gastrulation [15].

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A key feature of septin loss in both collective and individual cell movement is a failure to restrain cell membrane dynamics. In gastrula mesenchyme cells, this phenotype is manifested by the rapid formation and resolution of intercellular gaps [11]. In individual migrating myeloid cells, the loss of septin results in excessive membrane protrusion [16]. Curiously, loss of Wdpcp in gastrula mesenchyme also results in excessive membrane dynamics [11], though individual mouse fibroblasts lacking Wdpcp display reduced membrane dynamics [17].

In this report, we have explored the role of Wdpcp/Fritz in an intact epithelium. *In vivo* time-lapse imaging reveals a role for Wdpcp in restraining membrane dynamics specifically in the basolateral plasma membrane. These dynamics are dependent upon septins and actomyosin. These data provide new insights into a still poorly understood protein that links developmental signals (PCP) to the cytoskeleton.

2. Materials and methods

2.1. Embryo manipulations

Female adult *Xenopus laevis* ovulated with human chorionic gonadotropin. Then eggs were squeezed out to be fertilized using ground testis. The jelly layer of embryos was removed by using 3% cysteine (pH 7.9) at 2 cell stage. For microinjections, embryos were placed in a 2% ficoll in 1/3× MMR, and injected using forceps and an Oxford universal micromanipulator. The injected embryos were washed and reared in 1/3× MMR at stage 9. The muco-ciliary epithelium was analyzed at stage 26–27. Wdpcp-MOs was injected at 30–35 ng/blastomere.

2.2. Cloning, plasmids and antibodies

Translation-blocking morpholino-oligonucleotides (MO) was previously reported [11]. Wdpcp-MO sequence is 5′-ACAGCTCAGTCAGACAAAACGACAT3′. Septin2 cDNA was obtained from IMAGE consortium and subcloned into pCS107GFP-3STOP. Filamentous actin was stained with Alexa Flour 488-Phalloidin (Life Technology) as described [36].

2.3. Confocal imaging

For time-lapse imaging of muco-ciliary epithelium, embryos were immobilized by placing in a drop in 2% agarose, as described [20]. 20 μM Y27632 or 100 μM blebbistatin was treated for an hour before the time-lapse imaging. Y27632 was hold in the same position in the mounting dish and washed for an hour before taking the image. Image processing and image analysis were performed with LSM5, Image ProPlus, and Adobe Photoshop software. Blebbing index was determined as the ratio of total blebbing area within a single cell–cell contact compared to the length of that cell–cell contact.

3. Results and discussion

To assess the role of Wdpcp in the control of epithelial cell membrane dynamics *in vivo*, we took advantage of the frog *Xenopus*, which is closely related to mammals and whose large cell size and external development make them outstanding platform for live imaging of cell behavior [18–21]. In recent years, the *Xenopus* embryo ciliated epidermis has emerged as a powerful model for *in vivo* studies of mucociliary epithelia [22,23], and this tissue has contributed significantly to our understanding of the PCP proteins, including Wdpcp [11]. *Wdpcp* mRNA is highly expressed in *Xenopus* epidermis by RNAseq [24] and immunostaining has shown that Wdpcp protein localizes to the cell cortex throughout this epithelium [11]. We therefore chose to exploit this model tissue to examine the functions of Wdpcp in epithelia *in vivo*.

We have previously shown that antisense morpholino oligonucleotide (MO)-mediated knockdown of Wdpcp is highly effective and specific in developing *Xenopus* muco-ciliary epithelium [11], and these findings in *Xenopus* were subsequently confirmed by mutation of *Wdpcp* in mice [17]. We used the same strategy for Wdpcp knockdown and examined the effect on cell membranes in the *Xenopus* mucociliary epithelium by confocal microscopy. Wdpcp knockdown resulted in the formation of extensive gaps between neighboring cells; such gaps were not observed in control epithelia (Fig. 1A, a′ and B, b′, Supplementary Movies 1 and 2). When we quantified this phenotype (see Section 2), we found a statistically significant difference between controls and knockdowns (D). The MO used for Wdpcp knockdown was previously validated in *Xenopus* embryos [11], but as a further control for

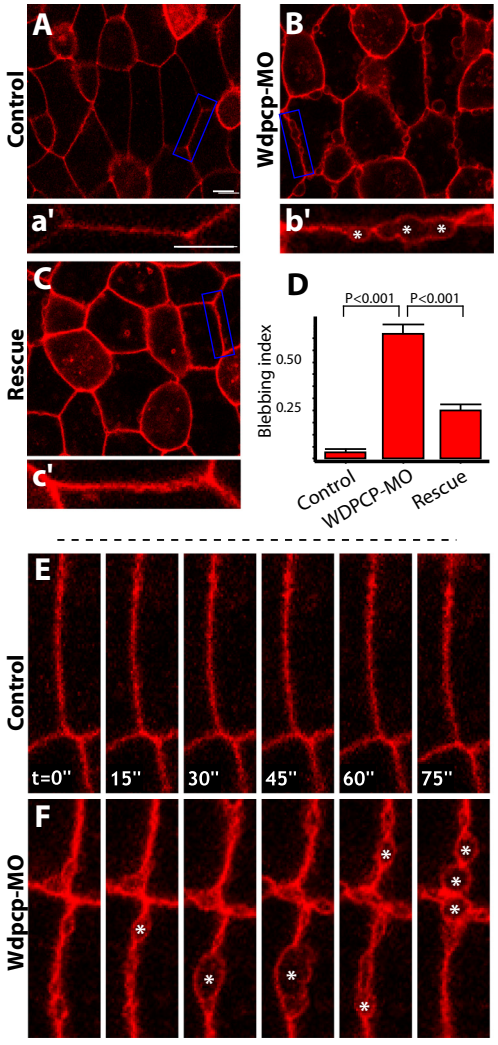

Fig. 1. Wdpcp controls plasma membrane stability in epithelial cells. (A) Control tissue expressing membrane-RFP, cell–cell contact indicated by the blue box is shown in (a′). (B) Morphant tissue showing severe membrane blebbing. The boxed region is shown in (b′) with higher magnification. Asterisks indicate blebs. (C and c′) Co-injection of Wdpcp-MO and Wdpcp mRNA (300 pg) rescued the membrane blebbing. (D) The quantification of membrane blebbing. Blebbing index was determined as the ratio of total blebbing area within a single cell-contact compared to the length of that cell–cell contact. Control $n = 125$; Wdpcp-MO $n = 196$; Rescue $n = 131$. The scale bars are 10 μm. (E) Still frames from a time-laps movie of control epithelium (Supplemental time laps Movie 1). (F) Still frames from a time-laps movie of Wdpcp morphant epithelium (Supplemental time laps Movie 2).

specificity, we observed that co-injected GFP-Wdpcp strongly abrogated this membrane phenotype (Fig. 1C).

To examine the phenotype Wdpcp knockdown further, we performed *in vivo* time-lapse confocal microscopy [20]. Time-lapse movies revealed that the observed intercellular gaps were highly dynamic, forming and resolving constantly along all cell–cell boundaries throughout the epithelium (Fig. 1E, F and Supplementary Movies 1, 2). This phenotype of rapid intercellular gap formation and resolution is similar to that observed following Wdpcp knockdown in gastrula mesenchyme cells [11].

Cell–cell adhesion differs substantially between such mesenchymal cells and epithelia, with the latter being joined predominantly by apically-positioned adherens and tight junctions. 3D time-lapse movies revealed that the observed defects in cell membrane stability in epithelial cells after Wdpcp knockdown were restricted to the basolateral cell membranes (Fig. 2). At the level of the apical epithelial junctions, no gaps were observed between cells in either controls or in Wdpcp knockdowns (Fig. 2A and B). By contrast, in more basolateral regions, obvious gaps were observed between Wdpcp knockdown cells, but not between basolateral regions of control cells (Fig. 2a′ and b′). This phenotype was also obvious in orthogonal views of the 3D datasets (Fig. 2C, c′ and D, d′; Supplementary Movies 3 and 4).

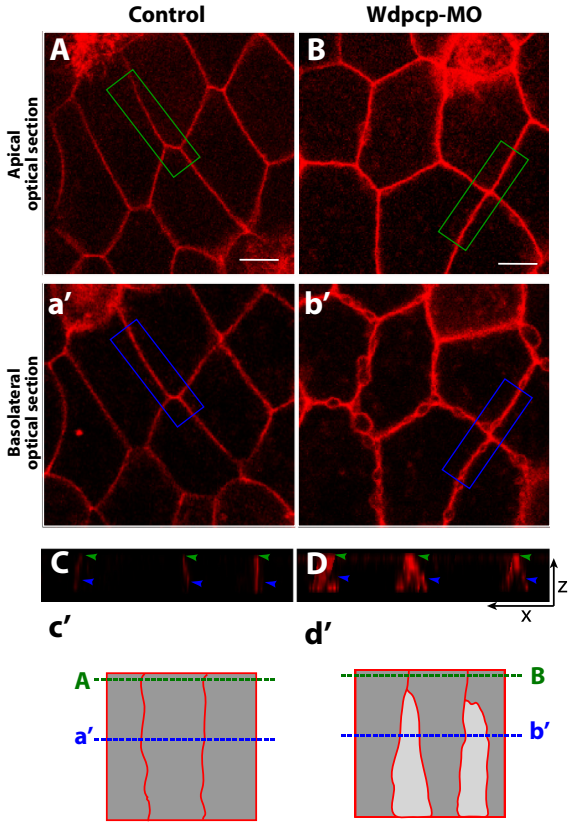

Fig. 2. Wdpcp knockdown caused severe membrane blebbing exclusively at the basolateral membrane. (A) The apical plasma membranes in control *Xenopus* epidermal epithelium, showing tight cell–cell contacts. (a′) The basolateral membranes of cells shown in panel (A) are also remain stably connected (B). The apical membrane of Wdpcp morphant tissue was indistinguishable from the control apical membrane. (b′) Wdpcp morphants displayed severe blebbing of the basolateral membranes. (C) *X–Z* projection of control epithelium. Green arrowheads indicate apical junctions. Blue arrowheads indicate basolateral membrane. (D) *X–Z* projection of Wdpcp morphant epithelium. Blue arrowheads indicate blebbing basolateral membrane while the apical junction is quite stable (green arrowheads). The scale bars are 10 μm. (c′ and d′) The drawing indicating the optical sectioning points for confocal imaging of (A and B) (Green lines) or (a′ and b′) (Blue lines).

In previous work, we found that Wdpcp controls the cortical localization of Sept2 during collective cell movements in mesenchymal cells [11]. Accordingly, we observed a consistent failure of Sept2-GFP recruitment to the cell cortex in epithelial cells following Wdpcp knockdown (Fig. 3A and B). This result is consistent with Wdpcp mediating the known role for cortical septins in controlling cell membrane dynamics both *in vivo* and *in vitro* [11,16]. This result also has additional implications for ciliogenesis. Wdpcp is essential for ciliogenesis in both *Xenopus* and mice, where it controls septin localization to the ciliary base [11,17]. Septins are essential for ciliogenesis, as they form a diffusion barrier that governs ciliary protein localization [11,25]. However, because normal cell cortex tension is required for ciliogenesis [26], our data here indicate that Wdpcp and septins may also control ciliogenesis via their role in cell cortex dynamics.

Because our data suggest a broad role for Wdpcp in plasma membrane stability in both mesenchymal [11] and epithelial tissues (Figs. 1 and 2), we next sought to understand the molecular mechanisms underlying these cell cortex defects. Wdpcp is an effector of PCP signaling, which is generally considered to act via Rho and Rho Kinase to organize the actin cytoskeleton [15,27–29]. However, the role for septins in control of actomyosin appears to be cell type-specific [14,30], and in fact we found no noticeable effect of Wdpcp knockdown on apical junctional actin assembly (Fig. 3C and D). Moreover, septins could also control cell cortex dynamics via direct interactions with membrane, since purified septins alter the topology of lipid bilayers in cell-free assays [31].

Because membrane blebbing following septin knockdown in T-cells in culture is ameliorated by disruption of Rho Kinase [16], we asked if the same may be true for Wdpcp knockdown in

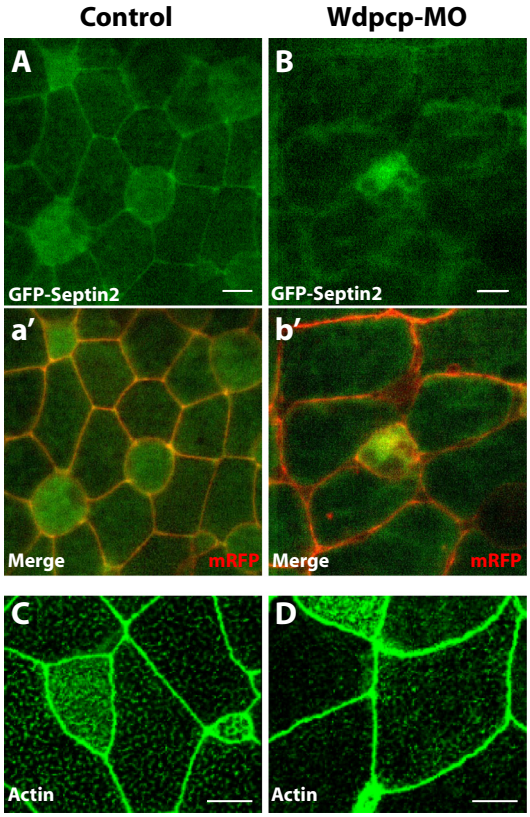

Fig. 3. Wdpcp is necessary for the cortical localization of septins to provide cortical rigidity. (A and a′) GFP-Septin2 localized to the cell membrane marked by memRFP. (B and b′) Knockdown of Wdpcp delocalized GFP-septin2 from the cell cortex. (C and D) Knockdown of Wdpcp expression did not disrupt cortical actin accumulation. Actin filaments were stained by phalloidin-Alexa488. The scale bars are 10 μm.

epithelial cells *in vivo*. Indeed, aberrant membrane dynamics in Wdpcp morphants were potently suppressed in the presence of the Rho kinase inhibitor Y27632 (Fig. 4A–D). The specificity of this suppression was confirmed by the resumption of membrane blebbing following washout of Y27632 (Fig. 4C and D). As a further test of the requirement for actomyosin in generating the membrane phenotype following Wdpcp knockdown, we found that the phenotype was also suppressed by inhibition of myosin II function with blebbistatin (Fig. 4D). This result is consistent with data from single cells lacking septin function [16].

Together, these data suggest that Wdpcp acts via septins and actomyosin to control cell cortex stability during epithelial homeostasis, a role very similar to that played by Wdpcp during collective cell movements in gastrula mesenchyme cells [15]. These data add to our growing understanding of the role of septins in controlling cell shape in diverse settings. For example, our data argue that septins suppress cell membrane dynamics in *Xenopus* epidermal cells, as they do in *Xenopus* gastrula mesenchyme cells and in mammalian T lymphocytes [15,16]. It will be of interest now to determine how these phenotypes relate to septin-mediated control of cell membrane structures in other cell types. For example, dendritic arbor complexity is substantially reduced following loss of septins, though mature spines are elongated [32,33]. Likewise, cell protrusive activity also appears to be reduced in *Caenorhabditis elegans* neurons lacking septins [34]. Our data also shed new light on the cell-type specific roles for septins in developing animals. For example, septins are implicated in activating myosin II activity in certain cell types [30], but suppressing it in others [14,15]. Likewise, a recent report has shown that following septin loss, cytokinesis proceeds normally in certain cell types, but not in others [35]. Together with our work during gastrulation [11,15], our data here suggest that Wdpcp may be a key nexus for the interaction between developmental signaling such as PCP and the cell biological machinery that executes cell-type specific behaviors.

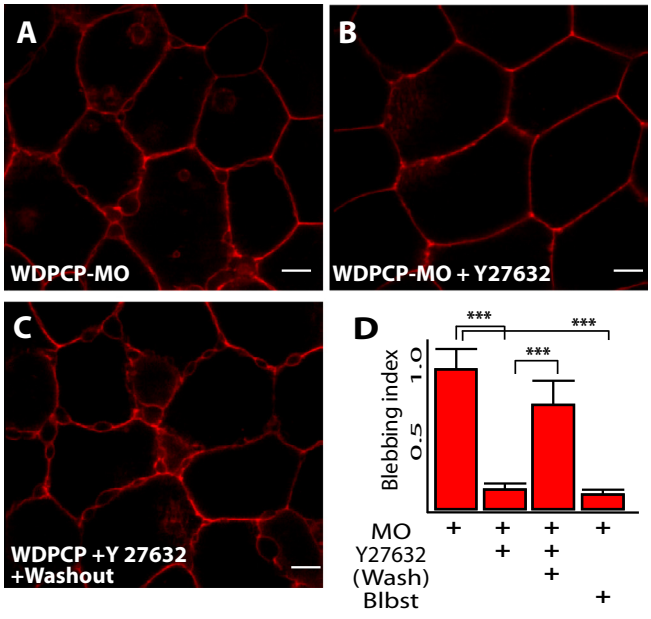

Fig. 4. Wdpcp maintains membrane stability via Rho Kinase and Myosin activity. (A) Epidermal tissue injected with Wdpcp-MO displaying severe membrane blebbing. (B) Y27632, a Rho kinase inhibitor, blocked the blebbing phenotype in Wdpcp morphants. (C) The same epidermis shown in B started blebbing again after 1 hour washout of Y27632. (D) Quantification of blebbing index; Wdpcp-MO $n = 24$; Y27632 $n = 44$; Wash $n = 23$; Blebbistatin $n = 83$. The scale bars are 10 μm.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.11.078.

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