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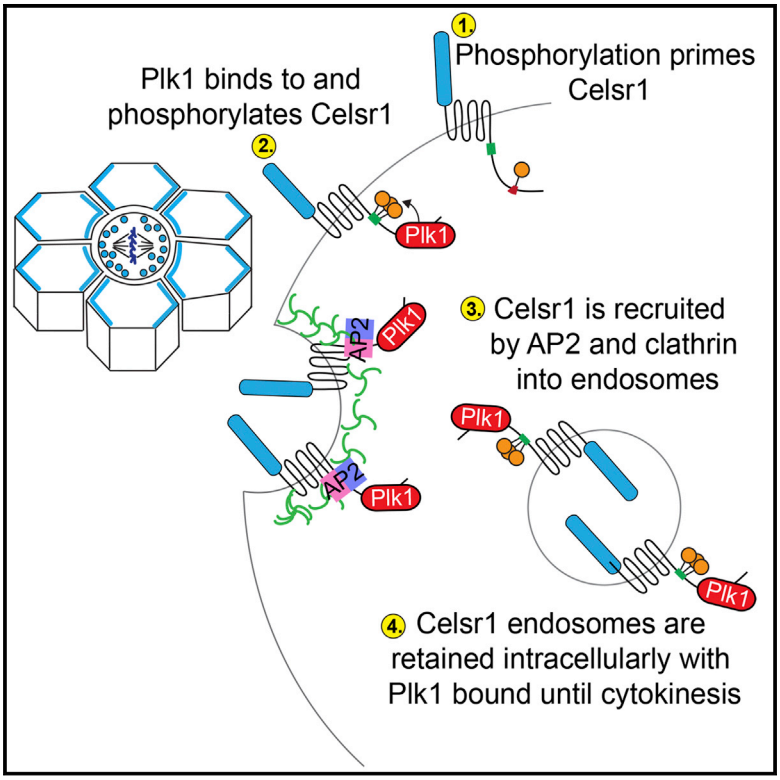
Developmental Cell

Mitotic Control of Planar Cell Polarity by Polo-like Kinase 1

Graphical Abstract



Highlights

- Plk1 localizes to mitotic endosomes and phosphorylates Celsr1's endocytic motif
- Plk1-dependent phosphorylation is necessary for Celsr1 mitotic endocytosis
- Celsr1 recruits Plk1 via a PBD-binding motif required for internalization
- Phosphomimetic mutations can uncouple Celsr1 internalization from mitosis

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In Brief

In polarized epithelial cells, planar cell polarity (PCP) proteins are internalized during mitosis and then redistributed with cell-cycle progression. Shrestha et al. now show that the mitotic regulator Polo-like kinase 1 (Plk1) coordinates this process via phosphorylation of the PCP protein Celsr1, which promotes Celsr1 endocytosis during mitosis.

Shrestha et al., 2015, Developmental Cell *33*, 522–534
June 8, 2015
http://dx.doi.org/10.1016/j.devcel.2015.03.024

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Mitotic Control of Planar Cell Polarity by Polo-like Kinase 1

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http://dx.doi.org/10.1016/j.devcel.2015.03.024

SUMMARY

During cell division, polarized epithelial cells employ mechanisms to preserve cell polarity and tissue integrity. In dividing cells of the mammalian skin, planar cell polarity (PCP) is maintained through the bulk internalization, equal segregation, and polarized recycling of cortical PCP proteins. The dramatic redistribution of PCP proteins coincides precisely with cell-cycle progression, but the mechanisms coordinating PCP and mitosis are unknown. Here we identify Plk1 as a master regulator of PCP dynamics during mitosis. Plk1 interacts with core PCP component Celsr1 via a conserved polo-box domain (PBD)-binding motif, localizes to mitotic endosomes, and directly phosphorylates Celsr1. Plk1-dependent phosphorylation activates the endocytic motif specifically during mitosis, allowing bulk recruitment of Celsr1 into endosomes. Inhibiting Plk1 activity blocks PCP internalization and perturbs PCP asymmetry. Mimicking dileucine motif phosphorylation is sufficient to drive Celsr1 internalization during interphase. Thus, Plk1-mediated phosphorylation of Celsr1 ensures that PCP redistribution is precisely coordinated with mitotic entry.

INTRODUCTION

Cell polarity is the fundamental unit of epithelial architecture, characterized by the asymmetric localization of cortical polarity proteins (Goodrich and Strutt, 2011; Roignot et al., 2013). When epithelial cells divide, they employ mechanisms to ensure these cortical asymmetries are preserved or tissues risk disorganization and loss of epithelial integrity. To preserve apical-basal polarity, the mitotic spindle aligns parallel to the substratum such that both daughter cells inherit cortical polarity proteins equally (Fernández-Miñán et al., 2007; Hao et al., 2010; Jaffe et al., 2008; Reinsch and Karsenti, 1994). We previously identified a mechanism whereby rapidly dividing basal cells of the mammalian skin preserve planar cell polarity (PCP) via mitotic internalization of cortical PCP components (Devenport et al., 2011). Mitotic internalization erases and restores PCP with every cell division and must therefore be precisely coordinated with cell-cycle progression, but the mechanisms regulating this process are not known.

PCP is defined by the collective alignment of cell polarity along the epithelial plane. The process is controlled by a set of conserved "core" PCP proteins, including Celsr (Flamingo/Fmi in *Drosophila*), Frizzled (Fz), Vangl (VanGogh/Vang), Dishevelled (Dvl), and Prickle (Pk), which orient diverse structures including *Drosophila* wing hairs and mammalian hair follicles (Goodrich and Strutt, 2011; Simons and Mlodzik, 2008; Vladar et al., 2009). PCP proteins localize asymmetrically within the cell, with Fz and Dvl positioned opposite Vangl and Pk (Axelrod, 2001; Bastock et al., 2003; Strutt, 2001; Strutt and Strutt, 2009; Tree et al., 2002). These complexes associate intercellularly via homotypic bridges formed by the seven-pass transmembrane cadherin Celsr/Fmi (Chen et al., 2008; Lawrence et al., 2004; Struhl et al., 2012; Usui et al., 1999). Local disruptions to PCP propagate non-autonomously to neighboring cells (Simons and Mlodzik, 2008; Taylor et al., 1998; Vinson and Adler, 1987), highlighting the need for PCP maintenance during tissue growth and regeneration.

In mammalian skin, PCP controls the coordinated alignment of hair follicles (HFs), which is maintained despite lifelong proliferation and regeneration (Devenport and Fuchs, 2008; Devenport et al., 2011; Guo et al., 2004; Ravni et al., 2009). HF alignment relies on PCP function in interfollicular basal cells, highly proliferative progenitors that give rise to the outer stratified skin layers and HFs (Devenport and Fuchs, 2008). When basal cells divide, asymmetrically localized PCP components become rapidly and selectively internalized into endosomes, segregated equally into daughter cells, and recycled to the plasma membrane where asymmetry is restored (Devenport et al., 2011). Forced cortical retention of PCP proteins during division causes tissue-wide defects in HF alignment, demonstrating the necessity of mitotic endocytosis to preserve global PCP.

To elucidate the mechanisms controlling PCP during mitosis, we undertook a proteomic approach to identify mitosis-specific posttranslational modifications (PTMs) and interacting partners of Celsr1. We demonstrate that the key mitotic kinase, Plk1, is a Celsr1-interacting protein essential for mitotic internalization. Celsr1 contains a conserved PBD-binding motif required for internalization and Plk1 association. Plk1 directly phosphorylates conserved serine/threonine (S/T) residues near Celsr1's dileucine endocytic motif, which allows the AP2 adaptor complex and clathrin to recruit Celsr1 into endosomes. Inhibition of Plk1 diminishes Celsr1 phosphorylation and blocks mitotic internalization, leading to the disruption of Celsr1 asymmetry ex vivo. Finally, mimicking dileucine motif phosphorylation uncouples Celsr1 internalization from mitosis and bypasses the