Filamin A–β1 Integrin Complex Tunes Epithelial Cell Response to Matrix Tension

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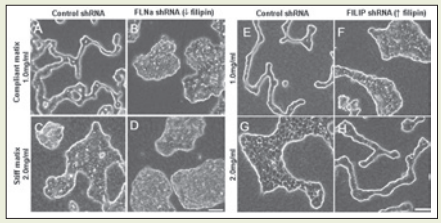
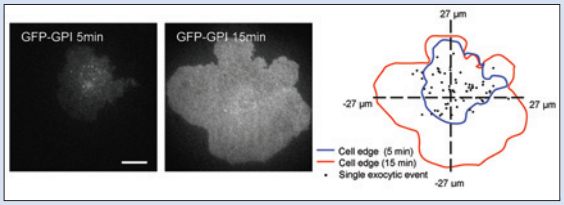


The compliance of the extracellular matrix and cellular regulation of matrix remodeling are critical determinants of tissue morphogenesis. Cells are able to "feel" the stiffness of their microenvironment and respond through mechanical feedback to regulate actin-myosin–based contractility and cell behavior. For example, mammary epithelial cells undergo ductal morphogenesis on compliant matrices but not on stiffer matrices that resist contraction. The mechanisms by which cells detect mechanical cues and transduce this information into biochemical signals are not well understood. Filamin A is an actin-binding protein and signaling scaffold that interacts with the cytoplasmic domain of β1 integrin to regulate integrin function. The authors use shRNA, expression of filamin, and specific reagents that disrupt or augment filamin binding to β1 integrin to demonstrate that enhanced filamin binding to β1 integrins enhances contraction of stiff matrices. It also rescues matrix remodeling and ductal morphogenesis, which are lost in stiff gels. These data suggest that filamin–β1 integrin complexes serve as part of the mechanosensitive machinery that both senses matrix tension and regulates collagen matrix contraction and cell morphogenesis in response to the physical properties of the matrix.



Plasma Membrane Area Increases with Spread Area by Exocytosis of GPI-anchored Protein Compartment

Nils C. Gauthier, Olivier M. Rossier, Anurag Mathur, James C. Hone, and Michael P. Sheetz

The mechanism by which cells control plasma membrane (PM) area is poorly understood. Changes in PM area cannot arise from stretching the membrane. One possibility is that folds in the PM flatten out to follow shape changes. This model would predict that membrane tension increases and limits the shape change induced by cell spreading. However, the authors found that PM tension decreased during spreading, indicating that PM area increased. Accordingly, exocytosis increased PM area by 40%–60% during spreading. Moreover the increase in PM area was proportional to the spread area. Golgi, lysosomes, and glycosylphosphatidylinositol-anchored protein vesicles (GPI vesicles) exocytosed during spreading, but no fusion of endoplasmic reticulum or vesicles containing transferrin receptor was detected. Microtubule depolymerization blocked lysosome and Golgi exocytosis but not GPI vesicle exocytosis or PM area increase. These data suggest that the dramatic increase in PM area during spreading originates selectively from a recycling pool of GPI-anchored protein vesicles.

Estrogen Inhibits ATR Signaling to Cell Cycle Checkpoints and DNA Repair

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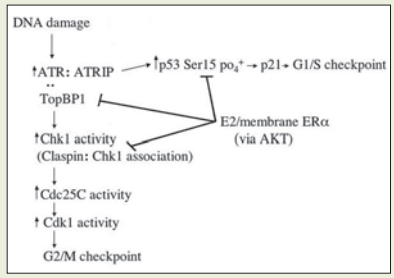
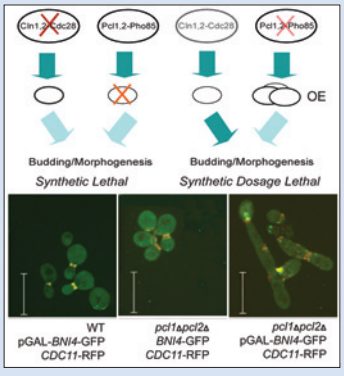


Estrogen and the estrogen receptor (ER) promote the development of breast cancer. Proteins that play roles in the growth and survival of breast tumors also respond to DNA damage. DNA repair mechanisms are essential to prevent the acquisition of transforming mutations and/or secondary mutations that enhance the aggressiveness of existing tumors. The ATR kinase cascade is rapidly activated in response to DNA damage, in part through its increased association with TopBP1. Downstream targets of ATR, including p53, function to promote the G1/S checkpoint and enable DNA repair. Here the authors show that estrogen, acting through plasma membrane–associated estrogen receptor ERα, triggers a signaling cascade that leads to phosphorylation of TopBP1 and inhibition of ATR kinase activity. Estrogen delayed assembly and resolution of DNA repair complexes, which was correlated with delayed DNA repair and excessive chromosomal damage. These new functions for estrogen may promote transformation of mammary epithelial cells or promote tumor biology by mutation acquisition.



Regulation of Cell Polarity through Phosphorylation of Bni4 by Pho85 G1 Cdks in *Saccharomyces cerevisiae*

Jian Zou, Helena Friesen, Jennifer Larson, Dongqing Huang, Mike Cox, Kelly Tatchell, and Brenda Andrews

For cell growth to proceed in an appropriate manner, the cell cycle regulatory machinery must be coupled to polarity progression. In *Saccharomyces cerevisiae* this requires the activity of one of two cyclin-dependent kinases (Cdks): Cdc28, which associates with cyclins Cln1 and Cln2; or Pho85, which associates with cyclins Pcl1 and Pcl2. Because both the kinases and their cyclins are redundant, identifying substrates has proved challenging. The authors addressed this redundancy problem by screening for genes that were synthetic lethal with one pair of cyclins and synthetic dosage lethal with the other. They identified the bud neck–localized adaptor protein Bni4 as a novel substrate of Pcl-Pho85. They also showed that phosphorylation in G1 by Pcl-Pho85 is required for Bni4 localization to the bud neck. Misregulated Bni4 appears to bind in an uncontrolled manner to an essential component that resides at the bud neck, causing catastrophic morphogenesis defects when overexpressed. ■