PIPKIN REGULATES E-CADHERIN ENDOCYTOSIS IN POLARIZED BREAST CANCER CELLS AND PROMOTES A SWITCH TO A MIGRATORY PHENOTYPE

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Introduction. The endocytosis, degradation, and recycling of cadherins is crucial for the dynamic regulation of adherens junctions and the control of cell-cell adhesion during tissue formation and in many pathological conditions. In order to allow for dynamic changes in intercellular adhesion, adherens junctions assemble and disassemble in a continuous fashion. A key mechanism for modulating adhesion strength is the adjustment of the cell surface levels of E-cadherin, the major component of adherens junctions. E-cadherin endocytosis, often accompanied by its degradation, has been observed in many developmental and disease processes and accounts for more rapid changes in adhesion strength that can occur independently of the transcriptional regulation of E-cadherin. However, the molecular mechanisms underlying E-cadherin endocytosis and recycling remain incompletely understood.

Materials and methods. To begin to examine the molecular mechanisms underlying E-cadherin trafficking, we used a combination of cell biological, biochemical and knockdown approaches in polarized MCF-7 breast cancer cells.

Results and discussion. Phosphoinositide signaling plays a key role in endocytic trafficking. We have previously shown that Type I beta phosphatidylinositol-4-phosphate 5-kinase PIPK1P, which synthesizes the second messenger phosphatidylinositol-4,5-bisphosphate PIP_2, regulates the turnover of focal adhesion complexes through the clathrin-mediated endocytosis of integrins (1,2). Here we show that PIPK1P also plays a role in the regulation of adherens junction turnover. Accordingly, a gain of PIPK1 в activity leads to the internalization and apparent degradation of E-cadherin, whereas the loss of PIPK1 в activity blocks the calcium-dependent turnover of adherens junctions and maintains E-cadherin localization at the plasma membrane. Consistent with a role in E-cadherin trafficking, endogenous PIPK1 в co-localizes with E-cadherin at cell-cell junctions and on intracellular vesicular structures. In addition, PIPK1e also regulates the turnover of tight junctions. Consistent with the idea that PIPK1e promotes the dissolution of cell-cell adhesions and a switch to a more migratory phenotype, we found that overexpression of PIPK1e in MCF-7 breast cancer cells results in cell scattering and the stimulation of cell migration and invasion.

Conclusions. Our data suggest that PIPK1(3 promotes the loss of the epithelial phenotype and the acquisition of a motile phenotype through modulation of adhesion receptor trafficking. These findings warrant further studies into the role of PIPK1e in the dynamic control of intercellular adhesion during developmental and disease processes, such as cancer metastasis.

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References.

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