LipidoDiv ANR JCJC-0089 (2007-2011)

Lipid and cytoskeleton remodelling during cell division

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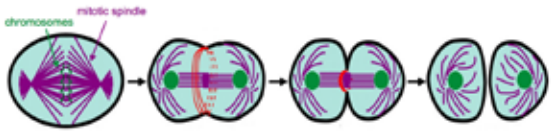
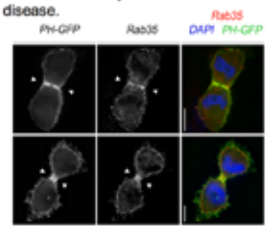
Background and Aims

Cell division and thus cell proliferation ultimately relies on cytokinesis, which leads to the physical separation of the two daughter cells at the end of mitosis. Robust cytokinesis is essential for maintaining genomic stability, and it has recently been demonstrated that a single defect in cytokinesis could promote tumorigenesis in mice. It is now apparent that intracellular traffic, including endocytosis and exocytosis, as well as lipids play a key role during cytokinesis abscission. Rab proteins are keys regulators of intracellular transport and our previous studies have identified the Rab35 GTPase as essential for the initial intercellular bridge stability as well as for promoting later cytokinesis abscission (Kouranti et al. Current Biology, 2006). Our aim is to address the fundamental question of how the cell cortex is dynamically polarized, how cell membranes/lipids are constantly remodelled and how these events control specific cytoskeletal elements in the context of cell division. In particular, several key questions are still unanswered: What is the nature of the transported cargoes essential for cytokinesis and what are their precise roles? What mechanisms control the temporal/spatial activation of these pathways? How is the coordination of the different transport pathways achieved? How could membrane traffic and specific lipid remodelling contribute to cytokinesis abscission and thus to the actual separation of the daughter cells? What is the repertoire of genes essential for cytokinesis abscission? What are the consequences of cytokinesis abscission defects *in vivo*?

Results

We found that the PI(4,5)P2 5-phosphatase OCRL, which is mutated in Lowe syndrome patients, is an effector of the Rab35 GTPase in cytokinesis abscission. GTP-bound (active) Rab35 directly interacts with OCRL and controls its localization at the intercellular bridge. Depletion of Rab35 or OCRL inhibits cytokinesis abscission and is associated with local abnormal PI(4,5)P2 and F-actin accumulation in the intercellular bridge. These division defects are also found in cell lines derived from Lowe patients and can be corrected by addition of low doses of F-actin depolymerization drugs. Our data demonstrate that PI(4,5)P2 hydrolysis is important for normal cytokinesis abscission in order to locally remodel the F-actin cytoskeleton in the intercellular bridge. It also reveals an unexpected role of the phosphatase OCRL in cell division and sheds new light on the pleiotropic phenotypes associated with the Lowe disease.

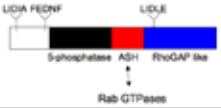




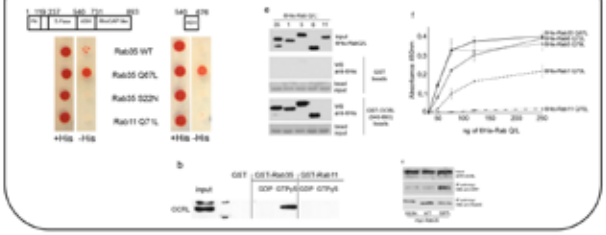
OCRL
Oculocerebrorenal syndrome of Lowe

$H_2O + PI(4,5)P_2 \longrightarrow PI(4)P + Pi$

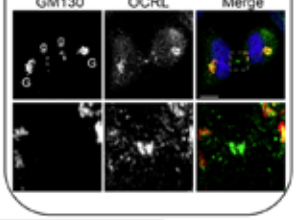
Phosphatidylinositol 4,5 bisphosphate 5-phosphatase



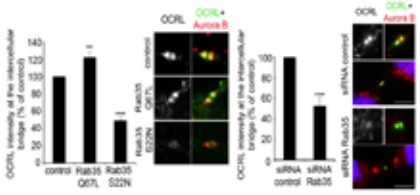
1. OCRL directly interacts with GTP-bound Rab35



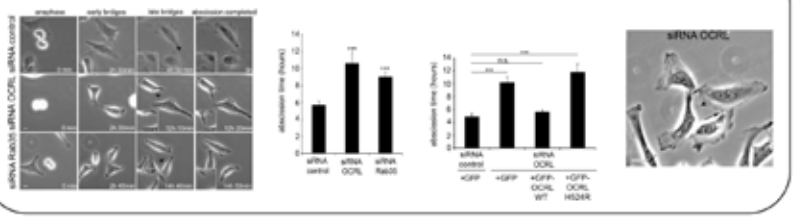
2. A pool of OCRL is localized at the intercellular bridge



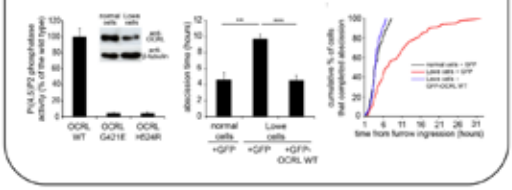
3. Rab35 activation controls OCRL localization at the intercellular bridge



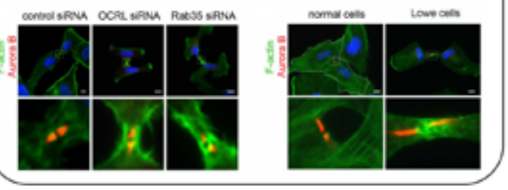
4. Cytokinesis abscission is defective in OCRL- or Rab35-depleted cells



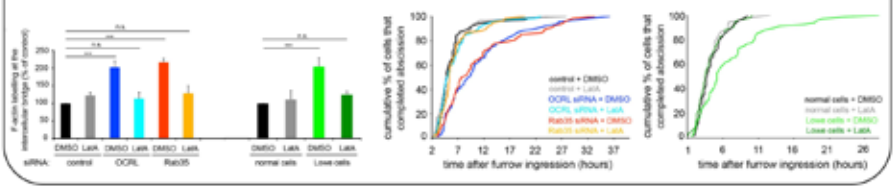
5. Cytokinesis abscission is defective in Lowe patient cells



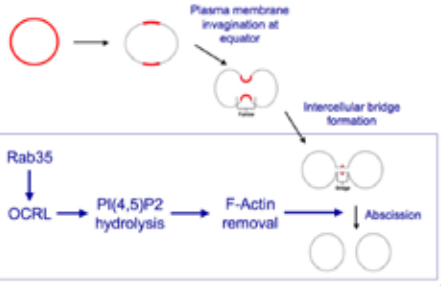
6. Abnormal accumulation of PI(4,5)P2 and F-actin at the intercellular bridge in OCRL- and Rab35-depleted cells



7. Abscission defects in OCRL- and Rab35-depleted cells are suppressed by low doses of the F-actin depolymerizing drug Latrunculin A



Conclusions



Perspectives

These results raise the possibility that other phenotypes associated with OCRL inactivation (e.g. the renal Fanconi syndrome) may be also corrected by reducing excessive F-actin levels and could represent a potential therapeutic lead, as recently suggested for other diseases. This will be tested in a recently established mice model for the Lowe syndrome.

Publications arising from the ANR support

CARRENO S, KOURANTI I, SZAFER GLUSMAN E, FULLER M.T, ECHARD A / PAYRE F. Moesin and its activating kinase Slik are required for cortical stability and microtubule organization in mitotic cells. (Echard and Payre are co-last authors) Journal of Cell Biology 180: 739-46 **(2008)**

MONTAGNAC G, ECHARD A AND CHAVRIER P. Endocytic traffic in animal cell cytokinesis. Current Opinion in Cell Biology 20: 454-61 **(2008)**

MISEREY-LENKEI S, CHALANCON G, BARDIN S, FORMSTECHER E, GOUD B AND ECHARD A. Rab and actomyosin-dependent fission of transport vesicles at the Golgi complex. Nature Cell Biology 12: 645-54 **(2010)**

DAMBOURNET D, MACHICOANE M, CHESNEAU L, ROCANCOURT M, FORMSTECHER E, SALOMON R, GOUD B AND ECHARD A. Rab35 GTPase and OCRL phosphatase remodel lipids and F-actin for successful cytokinesis. Nature Cell Biology in press **(2011)**

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