Apical-polarity membrane scaffolding proteins in endo- and epithelial cells

Supervisor/s:

Prof. Dr. Petra Knaus, FU Berlin
Project A20

Collaboration Project/s (if applicable):

Prof. Dr. Helge Ewers, Project A20
Prof. Dr. Volker Haucke, Project A01/07
Prof. Dr. Michael Krauss, Project A11

Abstract:

All cell types polarize, at least transiently during cell division or to generate specialized shapes and functions. The small GTPase Cdc42 plays a central role in cell-polarity control and integrates many signal transduction pathways on spatial and temporal levels. Cdc42 is a member of the Rho GTPases, whose members are regulated via GEFs (stimulate nucleotide exchange) and GAPs (trigger GTP hydrolysis). Cdc42 mutants cause loss of polarity in epithelial cells, aberrant paracellular permeability and mixing of apical and basolateral components. Tight junctions (TJ) are localized sub-apically and contain the PDZ proteins of the Par3 complex to which Cdc42 is recruited in its GTP-bound form via Par6. The scaffolding protein AMOT specifically targets to TJ and regulates Cdc42 and apical polarity proteins[1]. The N-terminal CC region of AMOT functions as a BAR domain, sufficient for Cdc42 regulation via inhibition of the GAP. Cdc42 and Par proteins stabilize dynamic cell junctions through regulation of apical endocytosis[2]. Borg proteins are effectors of Cdc42 and are also called Cdc42-EP1-5. They are involved in cytoskeleton remodeling and signaling, and their role in cell migration and differentiation highlights the importance of these proteins in physiological and pathological processes including angiogenesis. Most Borg proteins have been shown to form filamentous structures that co-localize with actin and septin fibers. Some septins (e.g. Sept9) bind F-actin and promote bundling of preexisting actin filaments. Borg proteins bind to both F-actin and septins to act as adaptor proteins that reinforces both networks[3].
We have shown in A20 that (a) BMP receptors interact with membrane-proximal septin filaments, (b) that Cdc42 and Borgs meet by binding to an activated heteromeric BMP receptor complex, (c) that the distribution of BMP receptors in endothelial and epithelial cells is polarized and (d) controls the barrier function via the activation of src kinase[4]. More recent results indicated AMOT to mediate apical BMP signaling.
By investigating the functional and spatial distribution of BMP receptors, Cdc42, Borg and AMOT in polarized endothelial and epithelial cells we aim at unraveling the role of these membrane scaffolding protein complexes in response to BMP stimulation.

Publication/s:

1. Wells CD et al., a Rich1/AMOT complex regulates the Cdc42 GTPase and apical-polarity proteins in epithelial cells. ***Cell,*** 2006
2. Harris KP et al., Cdc42 and Par proteins stabilize dynamic adherens junctions in Drosophila neuroectoderm through regulation of apical endocytosis. **J Cell Biol**, 2008
3. Calvo F et al., Cdc42EP3/BORG2 and septin network enables Mechano-transduction and the emergence of cancer associated fibroblasts. **Cell Rep,** 2015
4. Benn A., et al VE-cadherin facilitates BMP-induced endothelial cell permeability and signaling. **J Cell Sci,** 2016