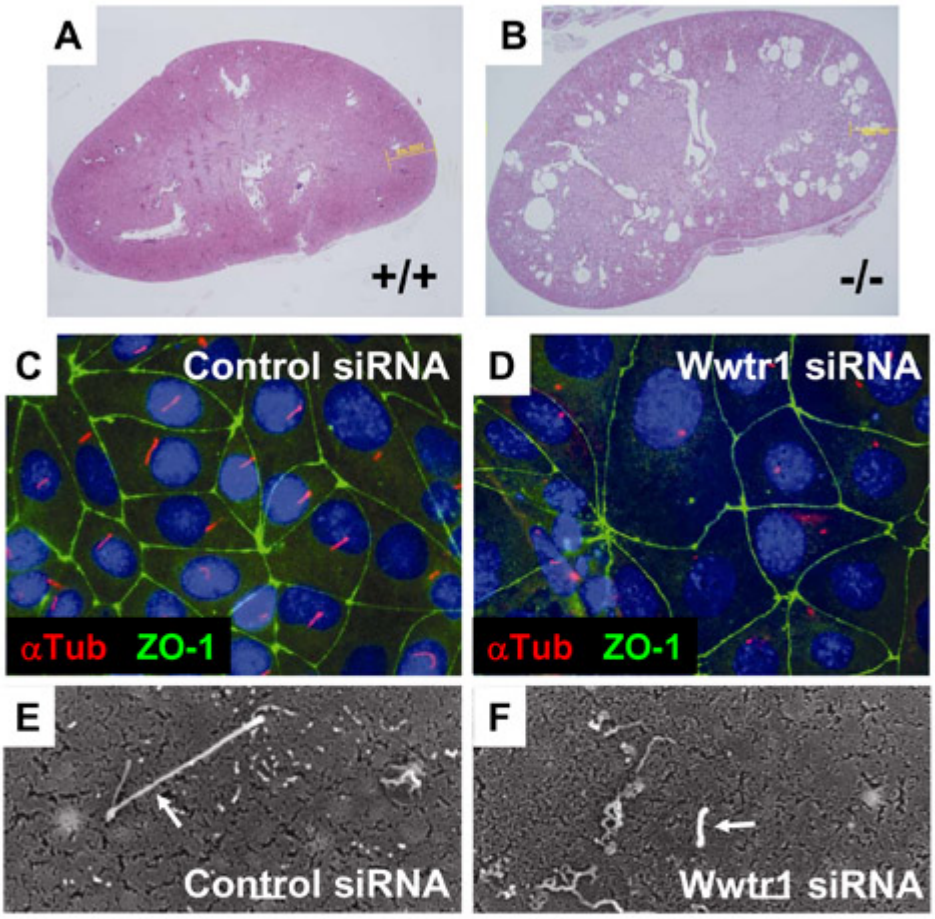
Research

Epithelial Polarity in Disease and Tissue Regeneration

Epithelial cell polarity Simple epithelia are organized into sheets of contiguous cells that cover surfaces of organs to separate external from internal compartments. Junctional complexes such as adherens and tight junctions (TJ) promote cell-cell adhesion. Epithelial cells exhibit a structural asymmetry of the cytoplasm and the plasma membrane is compartmentalized into distinct apical and basolateral domains with characteristic lipid and protein compositions.
Tight junctions In addition to promoting cell-cell adhesion, TJ restrict the diffusion of membrane proteins and lipids between the apical and basolateral plasma membrane domain. Furthermore, they regulate the paracellular permeability of the epithelial monolayer. TJ may also be involved in signal transduction events, possibly in response to cell-cell adhesion cues. Signaling pathways linked to TJ mediated cell-cell contact modulate epithelial cell polarity in normal processes (organ development and remodeling, wound healing) and their deregulation is likely involved in carcinogenesis. Dr. Hunziker and colleagues have identified

several proteins that interact with the TJ scaffolding proteins ZO-1, ZO-2 and ZO-3. The physiological role of these scaffolding proteins and their binding partners is characterized in cell culture and animal (mouse, zebrafish) models. In mice, for example, targeted disruption of the gene for one such protein, Wwtr1, results in a polycystic kidney phenotype. Renal cells of Wwtr1 KO mice show defects in cilia morphology. The group is also studying the function of the TJ transmembrane protein Claudin 16 (CLDN16) and how mutations in the corresponding gene lead to familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC). CLDN16 facilitaties the renal resorbtion of Mg2+ and Ca2+, which if defective results in excessive urinary Mg2+ and Ca2+ excretion, kidney stones and ultimately renal failure.

Membrane traffic and organization of the cytoskeleton In epithelial cells, newly synthesized proteins are sorted into distinct carrier vesicles for delivery either to the apical or basolateral cell surface. This group is analyzing how the exocyst (sec6/8 complex), required for exocytosis, targets vesicles to the plasma membrane and how small G proteins of the RGK family (Kir/Gem, Rad, Rem and Rem1) regulate exocytosis. RGK proteins also control actin and microtubule organization.
The laboratory expects to obtain insights into the development of renal pathologies and cancer by understanding how epithelial cell polarity is regulated.



(A, B) Longitudinal kidney sections from an 8-week-old WT and Wwtr-/- mouse, showing numerous cysts in the KO kidney. (C, D) Immunofluorescence microscopy of cells treated with control (Con-M) or Wwtr1 (Ri-10, B) siRNA for 72 h stained with Abs to acetylated α-tubulin (red) and ZO-1 (green) to label cilia and tight junctions, respectively. Nuclei were stained with DAPI (blue). Note a reduced number and shorter cilia on cells exposed to Wwtr1 siRNA. (E, F) SEM of a cell treated with control (Con-M) or Wwtr1 (Ri-10) siRNA for 72 h. Cilia (arrows) on Wwtr1 siRNA treated cells were often short with aberrant morphology if present, whereas control cells show intact long cilia.

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Vimentin Regulates Scribble Activity by Protecting It from Proteasomal Degradation

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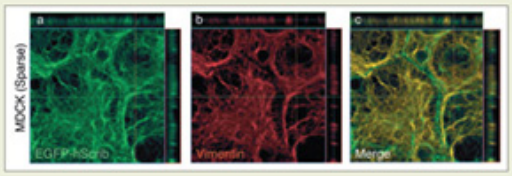

Cell polarization—the asymmetric distribution of cellular components into functionally separate regions—is fundamental to processes such as proliferation and movement. Its deregulation plays a central role in human diseases, in particular cancer. The multidomain protein Scribble (Scrib) is a key polarity regulator and neoplastic tumor suppressor in *Drosophila*. Mammalian Scrib is implicated in epithelial cell–cell adhesion and polarization during directed cell migration. The authors characterize a novel interaction between Scrib and the intermediate filament protein vimentin, which has a stabilizing effect on Scrib levels. Vimentin depletion results in the proteasome-dependent degradation of Scrib, which consequently leads to defective epithelial cell–cell adhesion and deregulated cell migration, closely phenocopying Scrib depletion. Double knockdown of Scrib and vimentin causes a phenotype similar to single silencing and suggests that the two proteins function in a single linear pathway. This stabilization of Scrib expression and function by vimentin is consistent with previously reported observations that vimentin is upregulated during epithelial wound healing. The findings imply a possible regulatory function for vimentin in Scrib homeostasis during epithelial migration.