Functional analysis of FilGAP in epithelial tubulogenesis

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Epithelial cells form a globular organ-like multi-cellular structure called cyst when cultured in extracellular matrix. The cyst generates extension followed by cell chains and tubules in response to hepatocyte growth factor (HGF). The Rho family small GTPases play essential roles for tubulogenesis. FilGAP, a Rac specific Rho GTPase-activating protein, is highly expressed in kidney. In this study, we examined the role of FilGAP in the tubulogenesis of Madin-Darby Canine Kidney (MDCK) epithelial cells. HGF induces basolateral extensions from cysts. Depletion of FilGAP by siRNA increased the number of extensions in response to HGF, whereas forced expression of FilGAP decreased the number of the extensions. FilGAP is phosphorylated and activated downstream of Rho-ROCK-signaling. Overexpression of phospho-mimic FilGAP (ST/D) mutant blocked formation of the membrane extensions induced by HGF in the presence of ROCK inhibitor, Y-27632. On the other hand, treatment of the tubules with Y-27632 induced scattering of the cells, but FilGAP (ST/D) blocked cell scattering and promoted lumen formation. Taken together, our study suggests that FilGAP may suppress formation of extensions whereas stabilize tubule formation downstream of Rho-ROCK-signaling.