Regulation of Cell Morphology by G Protein

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The small G protein ARF6 plays roles in regulation of endocytosis and activation of lipid signaling enzymes, such as phospholipase D and PIP5K, which produce lipid signaling molecules, phosphatidic acid and $PI(4,5)P_2$, respectively. We previously demonstrated that ARF6 plays a critical role in the regulation of cell morphology using cultured cells. In the present study, we describe the consequence of *ARF6* ablation in mice, in which manifests most obviously in the context of liver development. Livers from *ARF6*$^{-/-}$ embryos are smaller and exhibit hypocellularity, due to the onset of mid-gestational liver cell apoptosis. Preceding the apoptosis, however, defective hepatic cord formation is observed; the liver cells migrate abnormally upon exiting the primordial hepatic epithelial sheet, and clump rather than becoming dispersed. Consistent with this observation, the ability of hepatocyte growth factor/scatter factor (HGF) to induce hepatic cord-like structures from *ARF6*$^{-/-}$ fetal hepatocytes cultured *in vitro* in collagen gel matrix is impaired. Finally, we show that endogenous ARF6 in wild-type fetal hepatocytes is activated in response to HGF stimulation. These results provide evidence that ARF6 is an essential component in the signaling pathway coupling HGF signaling to hepatic cord formation. In this symposium, we will further discuss on the physiological functions of ARF6.