PRIMARY CILIA REGULATE cAMP-DEPENDENT SIGNALING IN KIDNEY CELLS

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Primary cilia are sensory organelles that project from the surface of most cells in the body. Renal tubular epithelial cell contains a primary cilium on the apical surface, and dysfunction of ciliary proteins has been implicated in the pathogenesis of polycystic kidney disease (PKD). *Kif3a* (Kinesin family 3a) encodes a subunit of the kinesin-II motor protein that is essential for the formation of primary cilia. We have previously shown that kidney-specific inactivation of *Kif3a* results in the loss of primary cilia and leads to kidney cysts. To understand the mechanism of the cyst formation, we generated *Kif3a* mutant renal tubular epithelial cell lines. Interestingly, the levels of cAMP were 40% higher in *Kif3a* null cells compared with control cells. Consistent with this finding, protein kinase A (PKA) activity and CREB-dependent gene transcription were also increased in *Kif3a* null cells. The specificity of cAMP signaling is generally achieved by compartmentalization in subcellular microdomains. We also found that adenylyl cyclases (AC) 5 and 6 were localized in primary cilia of renal epithelial cells. Moreover, the increased CREB activity in *Kif3a* null cells was normalized when AC5 was knocked down using siRNA. Taken together, these findings suggest that primary cilia regulate cAMP signaling through inhibition of AC5, and the loss of cilia may disrupt the microdomain that is required for proper regulation.