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Ischemia/Reperfusion-induced Alteration of Primary Cilium Length is Regulated by Reactive Oxygen Species

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The primary cilium is a microtubule-based non-motile organelle that extends from the surface of most mammalian cells, including renal tubular epithelial cells. Recent studies suggest that the primary cilium is associated with kidney diseases including acute kidney injury. Here, we investigated the alteration of primary cilium length during epithelial cell injury and repair following an ischemia/reperfusion (I/R) insult, and the role of reactive oxygen species and ERK signal in this alteration. Thirty minutes of bilateral renal ischemia increased plasma creatinine concentration (PCr) indicating severe renal tubular cell damage. Between 8 and 16 days following ischemia, the increased PCr returned to normal range without complete histological restoration. The primary cilium length was shortened at 4 h and 1 day, increased over normal tubules 8 days after ischemia, and then returned to normal length 16 days following ischemia. The primary cilium length of proliferating cells and mature cell was shorter than that in non-BrdU incorporating cells and differentiating cells, respectively. Treatment with Mn (III) Tetrakis (1-methyl-4-pyridyl) porphyrin (MnTMPyP), a superoxide dismutase (SOD) mimetic antioxidant, during the recovery of damaged kidneys accelerated normalization of primary cilia length concomitant with a decrease of superoxide and lipid peroxidation levels, and morphological recovery in the kidney. A marker of ciliary fragment acetylated tubulin was detected at early time of 4 h and increased at 24 h following I/R insult in the urine indicating that deciliation is one of the causes of shortening of primary cilium. In the MDCK cells, hydrogen peroxide released ciliary fragment from cell to culture medium, and MnTMPyP inhibited the deciliation. Inhibition of ERK inhibited elongation of cilia in overconfluent MDCK cells and recovering MDCK cells from hydrogen peroxide-induced oxidative stress. Taken together, our results demonstrate that primary cilium length is removed by oxidative stress induced by I/R or hydrogen peroxide treatment. The length of primary cilia lengthens over normal range in differentiating tubule cells and returns to normal in mature tubule cells, suggesting that the length of primary cilium may be a marker of cell fate. In addition, the length of primary cilium appears to be regulated, at least in part, by reactive oxygen species through regulation of ERK activation.

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Primary cilia, Reactive oxygen species, Ischemia