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The role of the circadian clock system in the transition from acute kidney injury to chronic kidney disease

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Objectives: Recent studies suggest that circadian rhythms are an important factor in maintaining healthy kidney functions; however, its role in acute kidney injury (AKI) remains unclear.

Methods: To investigate the role of tubule-specific clock gene disturbance in hypoxic tubular injury, we created human proximal tubule-specific *BMAL1* KO cells using CRISPR-Cas9 gene editing. In mice, we also determined whether time-restricted feeding (TRF), a dietary strategy to enhance circadian rhythm, can have beneficial effect on recovery of ischemia reperfusion injury (IRI) or its progression to chronic kidney disease (CKD).

Results: *BMAL1* loss in tubule cells resulted in the upregulation of cell cycle regulatory gene (p21) and inflammatory genes (TNF-α and CCL4) mRNA expression, suggesting that *BMAL1* is a critical regulator of these genes. Exposure to hypoxia for 48 h resulted in more increased expressions of p21 in *BMAL 1* KO cells than in WT HK-2 cells, leading to higher expression of TGF-β. In addition, loss of *BMAl-1* led to significantly increased vimentin and decreased E-cadherin expression upon TGF-β stimulation, suggesting an aggravated epithelial-mesenchymal transition upon *BMAL1* deletion. To clarify the role of clock system in AKI, we also tested whether TRF can have a beneficial effect during recovery phase after IRI. Despite limited access to food, TRF for 4 weeks after IRI had no effect on the total intake or weight of mice. However, we observed that TRF significantly improved renal function on day14 and reduced renal fibrosis on day28, which suggests that enhancing clock gene oscillations through restoring fasting/feeding cycle has a protective effect in the AKI to CKD transition.

Conclusions: We identified an important role of clock system in hypoxic tubular injury and the effects of treatment targeting circadian rhythm in AKI. Our results can provide a new perspective for developing novel therapeutic strategies for AKI.