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Effects of Par1a Deletion on Tubulointerstitial Fibrosis in Folic Acid Mouse Models of Renal Injury

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Abstract

Chronic Kidney Disease (CKD) affects 1 out of 7 adults in the United States and causes significant morbidity and mortality. Development of tubulointerstitial fibrosis, and the accompanying loss of functional tubular cells, leads to CKD progression. The Notch signaling pathway is required for renal development, however, sustained Notch activation in adult mice induces tubulointerstitial fibrosis. Dual deletion of *Par1a* and *Par1b*, serine threonine kinases, in developing mouse kidneys impaired Notch activation and resulted in the formation of abnormal glomeruli and proximal tubules. Deletion of either *Par1a* or *1b* does not affect kidney development.We hypothesize that *Par1a* or *1b* deletion in mice would protect against folic acid (FA) induced tubulointerstitial fibrosis.

FA models of renal fibrosis were induced in *Par1a* WT and *Par1a* KO mice with intraperitoneal injections of 250 mg/kg FA dissolved in 300 nM NaHCO3. Mice were examined 7 days after injection—the time of earliest fibrosis and peak Notch expression. Sirius red collagen staining was used to quantify the severity of fibrosis. Immunohistochemical staining for Notch signaling components and Par1a were performed. It was observed that *Par1a* expression was increased after FA injection. Par1a colocalized in tubules with increased Jag1 expression. Sirius red staining demonstrated less fibrosis in Par1a KO vs. WT mice.

Together, our results suggest Par1a deletion may be protective against renal fibrosis. Par1-Notch interactions may be mediated by effects on Jag1. Par1-Notch signaling could be a novel target for therapeutic intervention and potentially attenuate CKD progression.

KEYWORDS: Par1a/MARK3; Notch Signaling; Renal Fibrosis; Chronic Kidney Disease

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ABSTRACT

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