

## **SIGNIFICANCE STATEMENT**

microRNAs (miRNAs), short, non-coding RNAs that inhibit mRNA translation, have been shown to be downregulated in tubulointerstitial fibrosis (TIF), yet they appear to be dispensable for proximal tubule function. This study reports that proximal tubules and collecting ducts exhibit distinct miRNA expression profiles. Suppression of miRNAs in collecting ducts, using three mouse models that lack key enzymes needed for miRNA function, spontaneously induces partial epithelial-to-mesenchymal transition (EMT) and results in progressive TIF and renal failure. Thus, downregulation of collecting duct-enriched miRNAs and the subsequent induction of partial EMT may be a new mechanism for TIF. The results suggest that the collecting duct may play a pivotal role in TIF initiation and progression.