Small RNAs Have a Big Effect on Polycystic Kidney Disease

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The discovery of microRNAs (miRNAs), a group of small noncoding RNAs, has revolutionized our understanding of post-transcriptional regulation. Although it was presumed for a long time that transcriptional regulation is the major factor in protein expression, it is now evident that stabilization of transcripts and translational efficiency are equally important. Since their initial discovery, miRNAs have been implicated in a multitude of cellular responses both during normal development and homeostasis as well as disease formation and progression. In fact, miRNAs have proven to be useful biomarkers for disease diagnoses and show early promise for therapeutics. Thus, it is very surprising that in one of the most abundant human diseases, polycystic kidney disease (PKD), miRNAs have thus far only been implicated intermittently and direct mechanistic data are scarce. The article by Patel et al. in this issue of JASN now demonstrates a direct link between cyst formation, miRNAs, and Polycystin-1, the gene most frequently mutated in human autosomal dominant PKD (ADPKD).

Patel et al. used one of the most fruitful approaches to explore the role of miRNAs in organogenesis—the conditional ablation of Dicer, a key enzyme in miRNA biogenesis. Inhibition of miRNA processing in the different compartments of the kidney identified a broad range of phenotypes. For example, miRNAs regulate podocyte homeostasis, prevent apoptosis in the metanephric mesenchyme, and protect proximal tubules from renal injury. In this study, mice lacking Dicer in kidney tubules and collecting ducts exhibit hydronephrosis, hydroureter, and cyst formation. Although a similar phenotype was reported previously, Patel et al. further extend their analysis to mechanistically explain the phenotype. Small RNA profiling identified multiple miRNAs downregulated in Dicer mutant kidneys. Focusing on miR-200, they could show that this miRNA family targets Polycystin-1 and interferes with tubule formation in IMCD3 cells. Together, these data suggest that kidney cyst formation in this mouse model is, at least in part, caused by upregulation of Polycystin-1.

One of the intriguing aspects of this study is the analysis of the miR-200 family in kidney tubules. miR-200 has previously been shown to maintain the epithelial character of the cells and prevents epithelial-mesenchymal transition (EMT). In fact, mere overexpression of miR-200 is sufficient to trigger mesenchymal-epithelial transition (MET), whereas loss of function causes EMT. Thus, it is not surprising that the miR-200 family is highly expressed in kidney epithelial cells. The unexpected finding in this study is that this miRNA family does not trigger EMT in kidney tubules. Dicer-deficient renal epithelial cells did not show changes in E-cadherin, Zeb1, Zeb2, Snail1, and Snail2 expression, all hallmarks of EMT. Moreover, even in kidney cell lines, loss of miR-200 was insufficient to induce EMT. This observation is in accordance with studies in Pkd1 mutant mice, in which miRNA profiling of the cystic kidneys revealed downregulation of the miR-200 family. Even though the epithelial cells lining the cysts in these mice are highly proliferative, no signs of EMT are observed. In fact, the induction of fibrosis by interstitial mesenchymal cells accompanying PKD is due to the cyst burden and not the transition of renal epithelial cells. Thus, it is not surprising that no known correlation exists between PKD and any form of cancer or increased rates of metastasis. Together, this argues that the miR-200 family is not a universal EMT modulator and that kidney epithelial cells are per se different from other epithelia. Alternatively, Patel et al. may have uncovered another essential role for miR-200, which is required for epithelial homeostasis and lies upstream of EMT. Such a function does not involve the EMT targets of miR-200, but instead a different set of genes that include Polycystin-1. It is tempting to speculate that this function of miR-200 on epithelial homeostasis is not only restricted to the kidney, but also applies to other epithelia. In the future it will be important to further elucidate this contribution of miR-200 on epitheliogenesis and its participation in other diseases besides PKD.

The other main insight from this study is that Polycystin-1 is a bona fide target of miR-200. Its expression is upregulated in Dicer mutant kidneys, suggesting that these changes are important for cystic malformations. This is in line with previous reports demonstrating that tight regulation of Polycystin-1 is important and not only too little but also that too much Polycystin-1 causes cyst formation in mice, miRNAs, in general, and miR-200, in particular, may be the factors that maintain just the right levels of Polycystin-1 and thereby fine tune its expression. In fact, miR-200 fulfills the

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criteria for such a regulator. The expression levels of miR-200 family members are highest in terminal differentiated renal epithelial cells (our unpublished observation). In contrast, the function of Polycystin-1 is primarily required during tubulogenesis. This is emphasized by the fact that eliminating Polycystin-1 during early kidney development causes cyst formation, but inactivation after postnatal day 14 does not. Adult mice only develop cysts upon kidney injury. This is presumably due to the dedifferentiation of renal epithelial cells and the requirement of Polycystin-1 to cease the repair process. However, it is still unknown how Polycystin-1 function is repressed in adult kidneys. It has been demonstrated that the gene expression profile of kidneys changes dramatically around postnatal day 14 and that this is responsible for the protection against cyst formation. One alternative, but not necessarily contradictory, view is that miR-200 prevents Polycystin-1 from being highly expressed in adult mice. The experiments in the study by Patel et al. did not address such a possibility, but it would definitely be of interest to examine if inactivating Dicer in adult mice is sufficient to cause cyst formation.

One other noteworthy aspect of the study by Patel et al. is the phenotype of the Dicer mutant mice is probably not due to the activity of one single miRNA on one single gene. Although the authors convincingly demonstrate that miR-200 targets Polycystin-1 and causes cyst formation in IMCD3 cells, they also speculate that multiple miRNAs and target genes are involved. They actually provide in silico and in vivo data showing that many genes involved in ADPKD, autosomal recessive PKD, and nephronphthisis are potentially targeted by miR-200. Moreover, Dicer mutants obviously do not only lack miR-200 activity but all of the other miRNAs as well. Indeed, at least one other miRNA family, miR-17, has also been implicated in PKD. Mice lacking the RNA-binding molecule Bicaudal-C (Biccl) develop kidney cysts due to their inability to antagonize the activity of the miR-17 miRNA family. Similarly to miR-200, miR-17 also targets multiple PKD genes and in particular its interaction with Polycystin-2 is regarded as instrumental for cyst formation.

Together, these data suggest that miRNAs act as a homeostatic rheostat in renal epithelial cells and that perturbation of it can cause/contribute to cyst formation. It will be interesting to see if one actually can establish a miRNA signature for PKD. Such a panel of miRNAs may have a better diagnostic value than the identification of the precise mutations in Polycystin-1 or Polycystin-2. This will provide a better understanding of the physiology of cystic renal epithelial cells and novel therapeutic angles to treat PKD.

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DISCLOSURES

None.

REFERENCES
