The value of extracellular miRNA in diabetic kidney disease

Diabetes affects almost 8.3% of the global population and is associated with significant microvascular (renal disease, blindness) and macrovascular (coronary artery disease, stroke, peripheral arterial disease) morbidities and increased mortality. Despite newly developed treatment modalities, 30–40% of patients with diabetes are at risk of developing chronic kidney disease (CKD), where 15–20% of those patients require routine dialysis [1,2]. The annual costs of treating diabetic CKD and providing dialysis for patients are at the order of US$29 and US$49 billion in the USA, respectively [3]. Attempts to mitigate the risk of developing CKD by intensive glycemic [4] or blood pressure [5] control, and treatment with inhibitors of the renin angiotensin aldosterone system [6], had limited success. The dominant paradigm on the progression of kidney ailment is albuminuria; however, 50% of diabetic patients with progressive CKD did not show significant albuminuria [7]. Therefore, a better understanding of the underlying mechanisms for the progression of kidney disease in diabetes is urgently needed to provide a better disease management and identify new therapeutic approaches. To noninvasively assess the pathological progression of kidney disease in diabetic patients is nontrivial. Analyzing urinal molecular changes, such as concentration of specific proteins or metabolites in urine is a direct and logical approach to assess the perturbation of molecular networks in the kidney; however, the results largely just reflect the functional aspect of the kidney. The blood, on the other hand, may provide information on the dysfunction of pancreatic tissue during the progression of diabetes and the effect of deregulated energy metabolism on other organs including the kidney. Recently a number of studies revealed the presence of stable RNA molecules especially miRNAs, a class of short (21–23 nucleotides long) non-coding regulatory RNAs, in various biofluids including urine and blood [8]. These circulating miRNAs are packaged in either lipid vesicles or complexed with proteins or lipoproteins to escape extracellular RNAse activity [9–12]. The functional aspects and mechanisms of how miRNAs are released into the extracellular environment are largely unknown. There are reports that suggest cells actively

KEYWORDS
• albuminuria • chronic kidney disease • miRNA • systems biology

“Although still at an early stage, RNA-based therapeutics may hold great promise treating diabetic kidney disease.”

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Evidence from experimental models and human biopsies indicate the involvement of miRNAs in a variety of renal diseases including polycystic kidney disease...
it is a common issue associated with miRNA measurement, especially for circulating miRNA. Some of these inconsistencies are simply caused by the quickly evolving nomenclature guideline, for example, the use of -3p and -5p instead of the asterisk sign for miRNA name, which creates some confusion concerning the identity of the specific miRNAs that are reported. In addition, the nature of the miRNA molecule – short sequence length and highly conserved family members, makes the design of specific probes or primers to measure particular miRNAs a challenging task. The lack of a specific assay causes significant measurement- and platform-associated differences. The type of sample included in the study, sample storage, handling conditions and even RNA isolation method all add additional variables on the accuracy of miRNA measurement. Therefore, it is important to understand the differences in sample type and measurement platform before combining or comparing different studies [19]. In the coming years, with increasing interest in circulating miRNA, it is very likely that a few cell-free miRNAs in either urine or circulation will be identified as diagnostically or prognostically relevant.

Although still at an early stage, RNA-based therapeutics may hold great promise treating DKD [20]. A number of in vivo studies have reported the accumulation of therapeutic synthetic RNA in the kidney which, although undesirable for other targeted organs, provides an opportunity for modulating certain diseases in the kidney using RNA. Once we understand how miRNA are involved in disease-associated networks, it may be reasonable to test the possibility of using synthetic miRNAs or anti-miRs (antisense of miRNA) to revert the perturbed pathways. Insofar as the combination of clinical observation, systems biology/bioinformatics and basic molecular research facilitate the discovery of relevant miRNAs, one may reasonably anticipate the successful translation into effective RNA-based therapies for DKD.

Financial & competing interests disclosure
The authors gratefully acknowledge the support of DOD research contracts W911NF-10-2-0111 and HDTM11-I-13-C-0055 (K Wang), grants from Science and Technology Program of Guangdong 2013B051000080 (Y He), International Science & Technology Cooperation Program of Dongguan 2013508152005 (Y He), Guangdong Medical College Integration of Industry, Education and Research C20130004 (Y He), National Science Foundation of China 81273166 (Y Ding) and International Science & Technology Cooperation Program of Dongguan 20135081520017 (Y Ding). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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EDITORIAL  Argyropoulos, Ding, Wang & He


