More microRNAs as biomarkers and hope for precision medicine in kidney diseases

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microRNAs (miRNAs/miRs) are very short (20–25 nucleotides) single stranded noncoding RNAs which have the complementary to the 3' untranslated regions (3' UTRs) of target messenger RNAs (mRNAs) and induce the degradation of target RNAs and inhibit the protein translation (1-3). Those tiny RNAs are playing critical roles in physiological, developmental and pathological conditions and in variety of the human diseases and can be useful as biomarkers for human diseases because of their stable existence in body fluids such as blood and urine (4,5). Recent advances in the sensitive and quantitative detection of miRNAs in human biofluids are making miRNAs as promising noninvasive biomarkers for human diseases (6,7). Functional relevance of miRNAs in kidney diseases and their usefulness as biomarkers have been suggested, too (8,9). Comprehensive profiles of miRNAs in urine, urinary sediment and serum from patients in specific stages of DN, fibrosis, renal function decline [glomerular filtration rate (GFR)], albuminuria or rapid progression to end stage renal disease (ESRD) have been reported (10-16). Precise diagnosis at the early stage of kidney diseases is expected to provide the effective prevention of the diseases. A recent report identified numerous known and unknown miRNAs in urine as biomarkers for diabetic nephropathy (DN) and lupus nephritis (LN) (17). The authors profiled 2,402 urinary miRNAs in patients with DN or LN, and compared them with healthy controls. In DN, miR-2861, miR-1915-3p, and miR-4532 were significantly decreased and related to glomerular filtration rate and interstitial fibrosis/tubular atrophy. In LN patients, miR-3201 and miR-1273e were decreased and related to glomerular inflammation. Several members of miR-30 family were increased in both DN and LN and associated with glomerular filtration rate and proteinuria. New miRNAs identified in this study may provide specific noninvasive detection of DN and LN.

So far, numerous reports have been published for pursuing miRNAs as biomarkers for kidney diseases (8-16,18). It is still not easy to reach the clear conclusion because of some conflicting reports. However, molecular mechanisms might be different from patient to patient even in the same kidney disease. Big variations are observed in patient groups and even in healthy groups while the authors used healthy "patients" (17). Thus, another difficulty may be the availability of real healthy individuals. Deviations in patients may be caused by the stages in the disease progression. Some miRNAs may be high in the early stage but low in the late stage (13,14,18,19). Significant differences between DN and diabetes patients, and LN and systemic lupus erythematosus were detected in the same report (17). Therefore, simple comparison between healthy group and disease group may not be enough but the stage specificity of miRNAs might have to be studied.

Targeting certain miRNAs by chemically-modified antisense oligonucleotides has been successful to reduce specific miRNAs and inhibit fibrosis and hypertrophy in mouse models of DN and fibrosis (20-26). Treating patients with such miRNA inhibitors has been under development and evaluated in some clinical trials (27,28). Therefore, early detection of kidney diseases is benefit to prevent progression to renal failure and dialysis.

Combinations of newly identified and known miRNAs

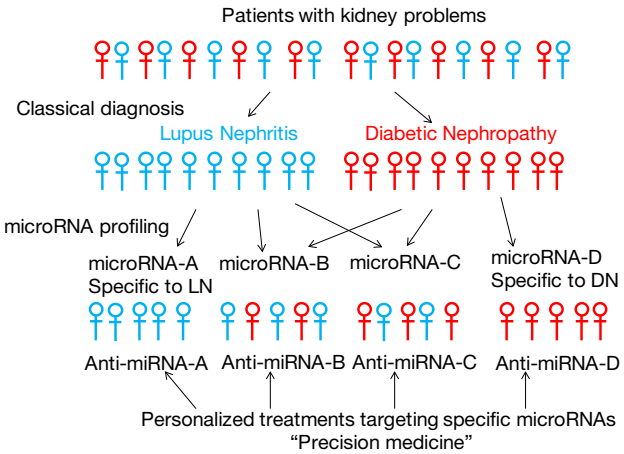

Figure 1 miRNA profiling for precision medicine. Patients with kidney problems are segregated to disease groups by classical diagnosis. However, patients can be separated to more groups by miRNA profiling and segregation might be different from classic methods. Some groups may be specific to DN (miRNA-A) or LN (miRNA-D) while some groups may be common to different diseases (miRNA-B&C). Based on segregation of patients, different treatments (specific miRNAs) may be possible. Targeting common miRNAs may be effective to treat patients in certain groups. Using more miRNAs and their combinations, more precise segregation of patients and miRNA-based precision medicine may be possible in the future. DN, diabetic nephropathy; LN, lupus nephritis.

may segregate patients more precisely to several groups even in single kidney disease and provide personalized treatments targeting specific miRNAs (*Figure 1*). On the other hand, some patients may be categorized in the same group by miRNA profiling even if they had different diagnosis (DN, DL or others) and the same treatment targeting common particular miRNAs may be effective to treat the patients who have been diagnosed as different kidney diseases (*Figure 1*). Changes in early stage may be an indicator of the initiation of kidney diseases. Some patients may need treatments even before the obvious symptoms such as proteinuria.

Accompanied by the development of recent technologies, the precise detection of miRNAs and suitable delivery methods are expected to be established. Hopefully, the diagnosis of patients by miRNA profiling and the treatment of patients by targeting specific miRNAs will be possible in the future for true personalized medicine (precision medicine) although much more efforts are necessary to identify miRNAs specific to diseases, stages or patients (individuals).

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Footnote

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