Editorial Commentary

Urine-based liquid biopsy: a new avenue for the management of renal cell cancer

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Renal cell cancers are frequent and lethal cancers (1). The majority of renal cancers are clear cell renal cell cancers. The diagnosis and treatment are dependent on imaging examinations (abdominal ultrasound and computerized tomography) and surgical removal of the tumor. Renal tumors are increasingly found because of frequent use of imaging examinations. However, not all of them are cancerous, as the proportion of benign tumors is about 10% to 15%. In particular for the tumors <4 cm, the proportion of benign tumors can increase to 20% to 30% (1). Therefore, a tissue biopsy is often performed to confirm a cancer diagnosis in order to avoid unnecessary surgical treatment (2,3). For the metastatic renal cancers, a tissue biopsy is also advocated before the targeted therapy. Unfortunately, the tissue biopsy is invasive and painful.

Liquid biopsy is a new notion developed in recent years (4,5). Liquid biopsies are intended to detect cancerous biomarkers in body fluids. Liquid biopsies have many potential advantages over tissue biopsies because they are less invasive and can be easily repeated. Blood is the mostly used fluid for liquid biopsy. Compared with the collection of blood, the collection of urine is completely painless and does not require medical personnel. It also allows for a large quantity of collection. Urine is a particularly interesting fluid as liquid biopsy for renal cell cancer because urine is the fluid of close contact with the renal tumor (6,7). The tumor biomarkers in urine may be more concentrated than in blood.

Circular RNAs (cirRNAs) are a class of conserved single-stranded RNAs that play an important role on cellular functions including the regulation of cancer driver genes (8,9). Their expressions can be tissue-specific or cell-specific (10). The study by Peter *et al.* investigated urinary cirRNA biomarkers for the detection of renal cell cancer (11). They observed significantly reduced levels of circEGLN3 and circSOD2 in urine from patients with a clear cell renal cell cancer when compared to healthy controls. The choice for urinary cirRNAs as molecular markers for renal cell cancer is interesting and reasonable, as cirRNAs have been shown to play an important role in renal cell cancer (12-14). The expression of circRNAs in urine may offer a new liquid biopsy for renal cell cancer. Previously, the circEGLN3 and circSOD2 biomarkers were shown to be upregulated in the tissues from renal cell cancer when compared to matched control tissues (12). It should be pointed out that urinary sediment was used in the study (11). Urinary sediment usually consists of exfoliated normal cells, tumor cells, immune cells, cellular debris and eventual bacteria. However, the tumor cells is unlikely shed into urine at the early stage of renal cancer patients. This is why cytology is not used for the detection of renal cell cancers.

Another compartment of urine is urine supernatant (15). Urinary supernatant is usually discarded. A future direction would be to study the urinary extracellular vesicles in urine supernatant (*Table 1*). Extracellular vesicles, which consist of exosome and microvesicles, are secreted into the body fluid by different cell types (16,17). Extracellular vesicles are considered as the treasures of biomarkers, which hold a great promise for cancer diagnosis and treatment. The study

Table 1 Urinary sediment and supernatant for the detection of renal cancer

Variables	Urinary sediment	Urinary supernatant
Targets	Tumor cells	Proteins, cell-free DNA/RNA, extracellular vesicles
Analysis methods	Cytology, molecular biology	Molecular biology, biotechnology
Advantages	Methods used in routine	Possible high abundance
Disadvantages	Lack of tumor cells	Clinical validation needed

of urinary exosomes has become explosive. The bilayer lipid membrane of exosomes considerably keeps the stability of the internal molecules such as RNA. Urinary exosomes are an excellent resource of liquid biopsy for kidney disease (18,19). Urinary exosomes may be abundant in cancer patients.

There exist some protocols for the isolation of urinary exosomes. These include ultracentrifugation, filtration, immuno-capture or precipitation (20,21). Ultracentrifugation isolation is considered as the standard technique for obtaining exosomes. However, it is not convenient to be used in the clinical laboratories. Some commercial kits for isolation of urinary exosomes have been available. Besides the new markers such as cirRNAs, the markers already found in tumor tissues are also possible paths to be explored in liquid biopsy in future (22). The isolation method of urinary exosomes suitable for clinical laboratory use remains the main challenge.

In conclusion, urinary extracellular vesicles hold a strong potential as clinically applicable "liquid biopsy". Significant progresses will be made in molecular biomarkers and appropriate biotechnologies. Urine-based liquid biopsy will provide a new avenue for the management of renal cell cancer.

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