

Urine exosome biomarkers: Taming the variability with normalization

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Non-invasive biomarkers for kidney disease are needed for accurate and timely diagnosis, including risk assessment, early diagnosis, prognosis of disease progression, recovery from kidney disease and/or response to therapy. In recent years, the field has focused on the most urgent need, early diagnosis, and a few promising early diagnostic markers are being developed for clinical use. Kidney biopsies can fill in some of the gaps, but they are rarely used beyond an initial diagnosis of kidney disease. Urine is a proximal fluid, enriched with biomarkers that are derived from kidney cells, which has the potential to provide kidney- and GU tract-selective biomarker candidates. While urine contains many kidney cell constituents, debris from damaged and dead cells can obscure information about the health status from kidney epithelial cells. In contrast, urine exosomes are small (~30-200 nm), intact vesicles, where intracellular contents are preserved, including mRNA, miRNA, and proteins, any of which can be promising biomarkers for kidney disease. Exosomes can come from any cell lining the nephron and can be readily separated from cellular debris. Urine volume can vary by over an order of magnitude, which can obscure the cut-off values for urine biomarkers. Biomarker excretion rate, the gold standard for urine biomarkers, can be obtained with a 24- hour urine collection. While accurate, this method is impractical for most patients and represents a significant barrier to widespread clinical adoption. Instead, if a biomarker value is properly normalized with an appropriate denominator value, a single “spot” urine collection can be used. Similarly, urine exosome excretion rates can vary by over an order of magnitude, which does not correspond to urine volume. Therefore, we examined normalization strategies for exosomal biomarkers in rats, and after kidney ischemia-reperfusion injury, we were able to identify a novel biomarker that was not statistically significant unless normalization was used.

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