Urinary Exosomes Join the Fight against Infection

James W. Dear
University of Edinburgh/British Heart Foundation Centre for Cardiovascular Science, The Queen’s Medical Research Institute, Edinburgh, United Kingdom

Urine is a complex fluid containing proteins, cells, nucleic acids, and a variety of extracellular vesicles. In the current issue of JASN, Hiemstra et al. demonstrate that exosomes, a specific type of extracellular vesicle, have antibacterial activity that could mediate host resistance to urinary tract infection (UTI). Given that UTI is the most common human bacterial infection (around 150 million cases annually), this new mechanism of urinary bacterial killing is an important discovery. However, researchers need new experimental tools to be able to move forward and understand the functional importance of exosomes in vivo.

Cells release lipid membrane–bound vesicles that can be broadly classified into two types: cell membrane–derived “microparticles” and exosomes, which originate from the cell’s endosomal system. A panel of physicochemical properties are measured to identify exosomes: they characteristically contain proteins involved in their intracellular formation (such as TSG101, ALIX, and LAMP1) and are approximately 20–200 nm in size, smaller than particles derived directly from the cell membrane. Exosomes that originate from the glomerulus and all regions of the nephron are present in urine. They contain protein, mRNA, microRNA (miRNA), and mitochondrial DNA from their kidney cell of origin. Therefore, urinary exosomes promise to be a productive reservoir for biomarker discovery, even a noninvasive replacement for the renal biopsy; however, this promise has not yet been translated into a biomarker with clinical utility (and this seems a long way off). The roadblock to clinical translation is partly caused by inadequate techniques for exosome isolation, which are too time-consuming in patients with cancer: A meta-analysis of randomised trials. Lancet 373: 1532–1542, 2009

and semiquantitative to form the basis of an assay that reliably informs time-critical clinical decision-making. In addition to being a source for potential biomarkers, exosomes might represent a cell-to-cell signaling mechanism because they can shuttle functional proteins, mRNA, and miRNA between cells in vitro. With regard to renal physiology and disease, exosomes can transfer aquaporin-2 from vasopressin-stimulated to unstimulated collecting duct cells, exosomes from injured tubular cells transfer miRNA into fibroblasts (resulting in cell activation), and stem cell–derived exosomes transfer mRNA to protect against AKI. Exosomes enter kidney tubular cells after injection into the systemic circulation. As a result, they represent a potential drug delivery system that can be engineered to deliver a complex package of RNA and protein that simultaneously targets multiple steps in an intracellular disease pathway.

Now a potential new role for urinary exosomes has been described: maintaining urine sterility by virtue of their antibacterial activity. Hiemstra and colleagues performed intelligent proteomic discovery studies and demonstrated that human urinary exosomes contain innate immune proteins with antimicrobial activity. Some of these proteins have previously been identified in human urinary exosomes, but, for the first time, the authors went on to demonstrate that exosomes can inhibit the growth of Escherichia coli (the major cause of UTI) and induce bacterial lysis. The authors included well-designed control experiments to reduce the risk that nonexosomal contamination was responsible for the observed biologic effects (a real risk for studies of exosome function), and this important work could be the first description of a new antibacterial host defense mechanism. The work leads to many intriguing questions, for instance, are there patients with exosome abnormalities that increase their risk of urinary sepsis?

However, the field of extracellular vesicle research has a key challenge to overcome: to determine whether the functions ascribed to exosomes in vitro have a significant physiological role in vivo. This is true for the antimicrobial activity described by Hiemstra et al. and for exosome-mediated cell signaling. To tackle this question, we need greater understanding of the pathways that control exosome loading with protein and RNA within the cell, the regulation of exosome release from cells, and the mechanisms by which exosomes bind and enter “recipient” cells or bacteria. Progress has been made, with recent studies demonstrating that the protein heterogeneous nuclear ribonucleoprotein A2B1 controls miRNA loading into exosomes and Rab guanosine triphosphatases regulate exosome release. Future insights into cell biology may facilitate the development of research tools that allow the function of exosomes in vivo to be dissected out. For example, if a drug could selectively inhibit urinary exosome excretion from kidney tubular cells, then the physiologic role of exosomes in preventing UTI could be determined.

Exosomes represent an exciting opportunity for new multimodality therapeutics, and the work of Hiemstra et al. expands their potential as a new class of antibiotic to treat UTI. In the future, exosomes could be manipulated such that the proteins on their surface selectively target the exosome to a specific cell type or bacteria, their miRNA cargo switches off specific disease pathways while the exosomal mRNA is translated to new “therapeutic” proteins. However, as is true for most of science, more research is needed.

DISCLOSURES
None.

REFERENCES
Reducing Avoidable Rehospitalization in ESRD: A Shared Accountability

Raymond M. Hakim* and Allan J. Collins†‡
*Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University, Nashville, Tennessee; †Department of Medicine, University of Minnesota, Minneapolis, Minnesota; and ‡Minneapolis Medical Research Foundation, Hennepin Health System, Minneapolis, Minnesota


The issue of rehospitalization captured the attention of hospitals and other health care providers when the Readmission Reduction Program was implemented on October 1, 2012, as authorized under Section 3025 of the Affordable Care Act. This program was based on a study of rehospitalization rates by Jencks et al., which highlighted inadequate care coordination by hospitals in Medicare patient hospital discharges, resulting in an approximately 20% readmission rate within 30 days of discharge. The Readmission Reduction Program established a Medicare diagnosis-related group (DRG) payment reduction for hospitals that exceeded the adjusted national average readmission rate for three diagnoses: acute myocardial infarction, congestive heart failure, and pneumonia. For fiscal year 2013, the potential reduction was up to 2% of the following year’s total DRG payments, and a further reduction of up to 3% of total DRG payments in fiscal year 2014.

Application of the high readmission penalty specifically to the dialysis population has also been proposed, based on the high rate of readmission noted by Jencks et al., and data reported by the US Renal Data System showing an overall rehospitalization rate for patients with ESRD of 34% within 30 days of discharge. This 70% higher rate of hospital readmission brought readmissions of the dialysis population into consideration for a quality metric of the Quality Improvement Program, which can affect up to 2% of the Prospective Payment System for dialysis.

The study by Erickson et al. in this issue of JASN highlights the potential relationship between the rate of readmission of dialysis patients and the frequency of face-to-face health care provider (physician and/or advanced practitioner) visits at the dialysis facility in the month after hospital discharge. The mean number of provider–patient interactions among patients who were rehospitalized or died within 30 days of hospital discharge was 2.1 ± 1.6 episodes, significantly below the frequency of 3.3 ± 1.2 episodes among patients who were not rehospitalized and did not die within 30 days of discharge. Among patients who were not rehospitalized, close to 65% were seen ≥4 times during those 30 days compared with 32.4% of rehospitalized patients. Instrumental variable regression analysis estimated that one additional provider visit (compared with the average of 2.8 ± 1.5 provider visits per month) may reduce the probability of rehospitalization by an absolute difference of 3.5%, or a relative reduction of 9.7% in the rate of rehospitalization. The authors further highlight the resulting economic health care benefits of an additional provider visit in the 30 days after hospitalization, which they estimate conservatively to be >$240 million in aggregate cost savings to Medicare funds.

It is evident that the increased frequency of nephrologist visits to the dialysis unit can be optimized with essential information from the discharging hospital, and timing of the additional visit based on the physician’s rounding schedule can be optimized by coordination with the discharge event. However, the association noted by Erickson et al. should be considered in any plan to reduce rehospitalizations in the dialysis population.

Maximizing the benefit of increased physician visits to dialysis patients after a hospitalization requires that critical information be transferred from the discharging hospital to the dialysis unit. Many hospitals have been reluctant to share the needed information with outside entities (e.g., dialysis facilities) because of concerns about Health Insurance Portability and Accountability Act privacy laws and lack of specific requirements for information transfer. The US Centers for Medicare and Medicaid Services (CMS) recently clarified in its interpretive guidelines for the new Conditions of Participation for hospitals that “the hospital must take steps to ensure that patients receive appropriate post-hospital care...” The guidelines clearly list dialysis centers among the specific outpatient facilities that hospitals are obligated to communicate with when a patient is discharged. These new Conditions of Participation should improve dialysis provider access to the required clinical information to promote care coordination between the hospital and the dialysis unit and allow for improved care and reduced risk of rehospitalization.

Other critical elements of the relationship between the frequency of the provider visits and rates of rehospitalization in dialysis patients are the timing of the visit (in relationship to the date of hospital discharge) and the focus of provider–patient interactions during the visit. A subanalysis of the 30-day readmission of hemodialysis patients regarding the relative frequency...