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

doi: 10.1681/ASN.2014020204

Urinary 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.1 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 20–100 nm in size, smaller than particles derived directly from the cell membrane.2 Exosomes that originate from the glomerulus and all regions of the nephron are present in urine.3 They contain protein, mRNA, microRNA (miRNA), and mitochondria 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 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.4 With regard to renal physiology and disease, exosomes can transfer aquaporin-2 from vasopressin-stimulated to unstimulated collecting duct cells,5 exosomes from injured tubular cells transfer miRNA into fibroblasts (resulting in cell activation6), and stem cell–derived exosomes transfer miRNA to protect against AKI.7 Exosomes enter kidney tubular cells after injection into the systemic circulation.8 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.9 As proof of concept, systemically administered exosomes, expressing a neuron-specific protein, delivered small interfering RNA to the mouse brain with a high degree of tissue specificity.10 If exosomes could be targeted specifically to diseased kidney cells, they could deliver protein and RNA to treat a wide range of abnormalities with minimal effects on healthy cells.

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,11 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 physiologic 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 exosomes12 and Rab guanosine triphosphatases regulate exosome release.13 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