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Novel Translational Approaches To Study Kidney Disease

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Editorial

Introduction

Research within the field of nephrology has significantly improved the well-being of individuals impacted by kidney disease. However, kidney disease is a still major healthcare problem that impacts more than 10% of the population and is responsible for increased healthcare costs and mortality worldwide[1]. Unfortunately, the precise mechanisms leading to kidney disease have not been fully elucidated. This *JoVE Methods Collection* highlights recent strategies to define kidney pathophysiology. Specifically, the research groups present a novel animal model and methods to evaluate or treat kidney disease using experimental models or clinical samples. The work presented in this collection is another series of excellent contributions to the field of nephrology and may provide new avenues to prevent, diagnose, or treat kidney disease in the future.

A translational animal model of acute kidney injury

Acute kidney injury (AKI) is a common form of kidney disease[2]. Several experimental models have been used to study renal ischemia/reperfusion (I/R) injury[3,4,5]. However, translating these findings to improve the clinical setting has posed many challenges since there are significant differences amongst species[6]. Doulamis et al. developed a swine renal I/R model using a bilateral balloon catheter to address this issue[7]. Their model was highly reproducible, caused reduced urinary output and estimated glomerular filtration rate, and increased plasma creatinine and blood urea nitrogen levels in animals. Further, gross tissue and histological examination revealed infarction and hemorrhaging within the kidneys. This new model is clinically relevant and may aid in further understanding AKI in humans.

Strategies to examine cellular mechanisms involved in kidney disease

Cytokines can contribute to kidney injury and repair[8]. Thus, it is important to identify the source and role of cytokines within the kidney. Taguchi et al. developed a technique to understand protein secretion using brefeldin A (BFA), a protein secretion inhibitor, in AKI and chronic kidney disease mouse models[9]. They injected BFA into the tail vein of mice and subsequently evaluated their kidneys using immunofluorescence staining. They determined that BFA inhibited protein secretion and caused cytokine buildup in certain cell types using cell-specific markers. This innovative protocol could be used to study protein secretion in several renal pathologies.

Another proposed mechanism thought to contribute to kidney disease is microRNAs (miRNA)[10], which are known to degrade and inhibit mRNA transcription. It has been reported that there is a correlation between miRNA expression in tissue and serum in humans[11]. However, there is no method to purify and quantify both mouse kidneys and serum miRNA. Yanai et al. optimized a quantitative real-time polymerase chain reaction method to evaluate miRNA expression in the kidney and serum of mice with age-dependent renal impairment[12]. They also established a correlation between both miRNA levels. This protocol is high-throughput and could be applicable to many pathological conditions.

New imaging techniques to evaluate kidney disease

Noninvasive imaging of the kidney can assess structural and functional defects. However, there are some limitations with the current methods. To circumvent this, Holmes et al. developed a simple, cost-effective 3D imaging technique based on robotic ultrasound (US) technology to quantify kidney, liver, and cardiac function[13]. Their protocol provided consistently high-quality images and could be used for studies where gross tissue, tumor sizes, or the benefits of therapeutics could be monitored. The greatest strength of this method is the high output of data. For example, three rats can be imaged at once, or 20–30 mice can be imaged per hour. This protocol is a quick alternative to traditional noninvasive imaging modalities.

Another research group in the collection used imaging to study unilateral ureteral obstruction (UUO), an injury model that induces surface glomeruli. Wagner et al. used intravital two-photon microscopy to monitor UUO in rats that develop surface glomeruli and those that do not develop surface glomeruli[14]. Two-photon microscopy provides an increased depth of penetration and examination of different regions of the kidney. The authors found that UUO induced inflammation and fibrosis, and also decreased red blood cell flow in rat kidneys. Quantifying blood flow, vasoconstriction, and dilatation in response to drugs and inflammation are a few benefits this method provides. Collectively, these studies provide new imaging strategies to study various tissues.

Estimating nanocrystalluria as a predictor of kidney disease

It has been proposed that assessing urinary crystals could be useful to predict kidney stone risk[15]. We developed a protocol to quantify urinary nanocrystals (≤1 µm) from healthy adults before and after they consumed a dietary oxalate load known to induce urinary oxalate levels[16]. We isolated and analyzed calcium-containing urinary nanocrystals using a calcium fluorophore and nanoparticle tracking analysis (NTA). We determined that NTA can specifically detect calcium-containing nanocrystals in urine, and the results were consistent with our previous findings[17]. This protocol can be used to study urinary nanocrystals in stone formers or various fields of research where crystalopathies occur.

Therapeutic approaches to treat kidney disease

Artificially synthesized miRNA mimics have been suggested as a possible treatment for kidney disease. However, serum RNAase can degrade exogenous miRNA mimics[18]. Yanai et al. produced non-viral vectors based on linear polymer, polyethylenimine nanoparticles (PEI-NPs), to safely deliver a miRNA mimic to the kidneys of mice[18]. They proved that the mimic was effective in overexpressing the targeted miRNA. The limitations of this method include the substantial amount of PEI-NPs required for larger animal models and the lack of specificity to the kidneys. However, based on the success of RNA vaccines, miRNA mimics could be an ideal therapeutic option for kidney disease.

Concluding remarks

The comprehensive research presented here introduces a new animal model and techniques to study prevalent issues surrounding nephrology. It is important to note that some of these methods could apply to other areas outside of nephrology. The next logical steps will be to investigate how these methods could be tested in larger animal models and clinical trials. We hope that the sharing of these protocols will expand our knowledge about renal pathophysiology and birth new ideas to mitigate kidney disease in individuals.

Disclosures

The authors have nothing to disclose.

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