

A new perspective on urinary proteomics and drug discovery in chronic kidney disease

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ABSTRACT

Heart Chronic Kidney Disease (CKD) is becoming a major public health issue around the world. The discovery of a specific collection of early biomarkers for CKD is critical for furthering disease understanding, enhancing diagnosis, treatment, or development, and monitoring drug efficacy. Because kidney

fibrosis is a common pathophysiological pathway to end-stage renal failure, regardless of the initial renal insult, these biomarkers are considered early tubulo-interstitial fibrosis biomarkers. The availability of a specialized collection of biomarkers for CKD is a requirement for developing and validating new devoted medications in clinics without having to wait years for a functional response in patients.

Key Words: CKD; Biomarker; Drug discovery; Urine; Proteomics

INTRODUCTION

Chronic Kidney Disease (CKD) is becoming a major public health issue around the world. Chronic progressive kidney failure affects roughly 8-10 percent of people in Western nations today and the spread of diabetes and metabolic syndrome among teenagers will exacerbate the situation in the coming years [1-3]. The discovery of a specific collection of early biomarkers for CKD is critical for furthering disease understanding, enhancing diagnosis, treatment, and medication development, as well as evaluating the efficacy of new therapies. Biomarkers and surrogate biomarkers are currently employed in clinical medicine for illness diagnosis, disease activity indicators, and therapy response prediction and monitoring. A biomarker is a parameter that is "objectively tested and assessed as a sign of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention," according to most definitions [4]. In therapeutic trials, a surrogate biomarker is described as "a laboratory measurement or physical indication that is employed as a substitute for a clinically significant end point that is a direct assessment of how a patient feels, functions, or survives and is predicted to predict the effect of the therapy [5]." Antinuclear Antibodies (ANA), Antineutrophil Cytoplasmic Antibodies (ANCA), and Antiglomerular Basement Membrane Antibodies (anti-GBM) are clinically recognised and validated indicators for disease diagnosis in autoimmune illnesses [6-8]. All of these signs are linked to the illness process, assisting clinicians in diagnosis and treatment selection. Furthermore, these markers provide for a straightforward evaluation process. While urine proteomics appears to be promise for identifying biomarkers, medication research in renal illnesses is far from pee-driven. In recent decades, historical advances have primarily focused on potential illness mechanisms, such as improved knowledge of immunological processes (steroids, immunosuppressors), or mechanisms customized to cells. Cyclosporin A, which affects the cytoskeleton of podocytes, and angiotensin-converting enzyme inhibitors, which influence renal hemodynamics while simultaneously inhibiting TGF β , are two significant exceptions. No therapeutical evolution has taken into account urinary biomarkers or stemmed from urine research. In the past, this failure was caused by a lack of controlled studies on urine composition in various diseases and technological issues, but we are now on the road to closing this gap.

Proteomics in urine

The hunt for such biomarkers in renal illnesses appears to be naturally geared toward urine analysis. Urine is plentiful and easy to obtain, necessitating noninvasive sample procedures and simple storage conditions, and it can be collected over time for clinico-pharmacological surveillance. Urine, like all body fluids, contains hundreds of proteins and peptides as a result of complicated filtration, secretion, and reabsorption processes that occur throughout the nephron. Proteins that are expressed throughout the body

and then exchanged into the blood compartment may show up in urine as peptide components or complete proteins. Proteomic technologies have the potential to transform clinical care by allowing for the discovery of protein biomarkers for diagnosis, disease progression prediction, therapy selection, and monitoring response to new pharmacological regimens. Recent technological and methodological advancements have made it possible to use urine as a source of potential biomarkers in proteomics research. Renal Fibrosis is a pathological condition that causes end-stage renal failure.

As previously noted, the progression of CKD to end-stage renal disease is independent of the initial renal insult, and tubulointerstitial fibrosis appears to be the common thread in CKD. The primary players in the fibrotic kidney are activated fibroblasts and myofibroblasts, which are rare and typically quiescent in the normal kidney. These cells become more proliferative, display the myofibroblast signature α -Smooth Muscle Actin (α -SMA) for the first time, and actively manufacture extracellular matrix components, resulting in tissue remodelling and chronic kidney failure.

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Clinical proteomics research prospects

The selection of patients to be included is a critical issue in revealing the proteome fibrosis fingerprint. Because fibrosis cannot be easily linked to any clinical parameter and biopsy remains the gold standard for fibrosis assessment, patients with idiopathic Chronic Kidney Disease (CKD) must be excluded for the time being and their analysis postponed until specific fibrosis biomarkers appear on the laboratory medicine scene. Patients with certain genetic abnormalities who have a verified record of biopsy indicating

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tubulo-interstitial fibrosis would be prioritised because they are regarded the actual genetic model of fibrosis. Because tubulo-interstitial fibrosis is the unifying feature and the graft is the clear trigger, recipients of renal grafts who are also carriers of Chronic Allograft Nephropathy (CAN) appear to be the most promising. Other pathologies would follow these early techniques, and the experimental paradigm for evaluating and validating data from specific situations would be used.

Analytical issues

To take things a step further, various technological challenges must be resolved before urine proteome analysis can be performed. The collection, concentration, desalting, and technique selection of urine samples are all substantial challenges. Previous studies review articles and recommendations by the European Kidney and Urine Proteomics Group (EuroKUP) have addressed urine variability, suggesting standardising shared procedures such as second morning micturition sampling without protease inhibitors addition and immediate freezing. In terms of urine preparation procedures, Thomboonkerd et al. pioneered the adsorption of urinary basic/cationic proteins on SP sepharose Fast Flow beads, demonstrating that enrichment techniques are generally applicable to urine [10]. This method has been shown to be capable of permitting the analysis of complicated fluids, such as cerebrospinal fluid, using an efficient and repeatable methodology using small amounts and without the need for substantial prefractionation. Exosomes, tiny cellular vesicles containing apical membrane and intracellular fluid produced from all cell types confronting the urinary space, were found to be both in vitro and in vivo biomarker candidates for structural renal injury. This strategy, when further studied with specific antibodies capable of trapping exosomes from different nephron segments, will considerably contribute to elucidating kidney pathology by limiting inquiry to a specific collection of proteins. Exosome enrichment, in contrast to CPLL, allows us to gain additional information into individual afflicted cells that release exosomes. However, current investigations are hampered in many cases by a lack of consistency in the isolation and purification procedures used, as well as a lack of agreement on purity requirements. The sample analysis methods chosen and the sample amplitude are also important considerations. The unique viable readout techniques are DEMS or CEMS, as the end desirable application is routine screening for such biomarkers in CKD patients treated with antifibrotic medications. Both allow for a fast and accurate one-step screening procedure that allows for high-throughput resolution of the urine proteome. The story's weakest feature is undoubtedly the sample amplitude for such CKD biomarker identification study. Unfortunately, the previously mentioned strict requirements, namely samples with a documented record of biopsy in the same cases repeated over time, severely limit the number of centres and patients who can be involved in a pilot research.

CONCLUSION

There is only one takeaway message. We must leave the tranquil harbour if we are to advance in our understanding of renal fibrosis pathophysiological processes and CKD medication development. To progress to chronic tasks and targets, close collaboration between professionals in nephrology, pathology, laboratory medicine, and proteomics is required, along with a strict patient selection criteria and considerable technical breakthroughs available for routine screening. The essential to bridging already existing acute kidney injury biomarkers is the availability of a sound and clear panel of biomarkers for early detection of renal fibrosis, why not uniquely

composed of proteolytic fragments of particular proteins. With recognized indicators of chronic kidney disease, kidney injury molecule-1, neutrophil-gelatinase associated lipocalinor IL-18. We believe that analysing selected cohorts of patients, such as transplanted patients and pure genetic models of fibrosis, is a viable way for achieving this goal. We might be able to pick out just biologically relevant indicators from huge lists of proteins found by mass spectrometry techniques if we use this two-pronged strategy. Genetic models may provide a limited list of possible biomarkers, but transplantation series may help confirm these biomarkers in fibrosis series that are not impacted by a particular pathway. Finally, samples from large biobanks containing a diverse panel of glomerular and tubular disorders would be employed for the requisite confirmation of fibrosis markers. Their contribution will be critical in tackling the problem of fibrosis and modulating a broad approach to renal disorders in the broad sense of the term. For the reasons stated above, we feel that a concerted effort should be undertaken to develop a uniform strategy for CKD biomarker research. The availability of a precise collection of CKD biomarkers is a prerequisite for developing new CKD medications and validating them in clinics without having to wait years for a functional response in patients. We believe that this is a point where we must all work together.

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