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Renal Transplantation and Urinary Proteomics

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1. Introduction

Urine is the terminal metabolites of bloodstream which is produced by filtration of glomerulus, and re-absorption, secretion and excretion of the renal tubule and collecting tubule (Figure 1), so that proteins found in serum may also be identified in urinary proteins. Urinary composition and properties can reflect the status of the entire urinary system, especially the changes in the type and quantity of proteins in the urine that carry information of the occurrence and development as well as prognosis of a variety of diseases of the urinary system, urine can also reflect relevant situation of other organs of the body. The source of urine is simple, convenient and non-invasive, easily accepted by patients, with no discomfort and contraindications. Therefore, uroscopy is one of the most common and important methods used to diagnose kidney and urinary tract diseases. In this sense, urinary proteome analysis can be used for the diagnosis and / or prognosis indicators of diseases.

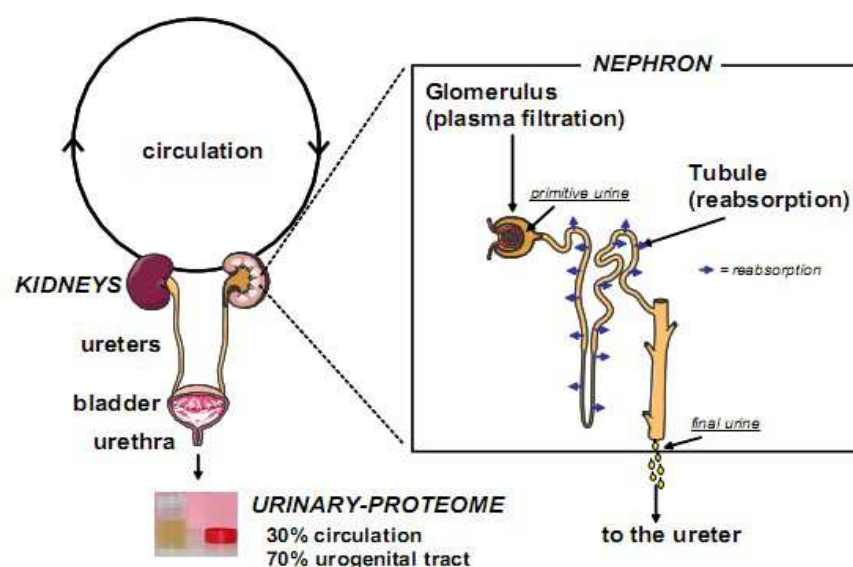


Fig. 1. 70% of the urinary proteins and peptides originate from the kidney and the urinary tract, whereas the remaining 30% originates from the circulation (Davis et al, 2001).

2. Methods of uroscopy

For diseases of urinary system, uroscopy is an important basis for diagnosis and is also of very important reference value for the diagnosis of certain systemic diseases and diseases of other organs of the body which affect the changes of urine, such as diabetes, blood diseases, liver and gallbladder diseases, epidemic hemorrhagic fever, etc. Meanwhile, the laboratory tests of urine can also reflect the treatment efficacy and prognosis of some diseases.

2.1 Urine routine examination

Uroscopy includes items of routine uroscopy, mid-stream urine culture (MSU), urinary three cups test, Addis count, quantitative test of urine protein and so on. The usually popular saying of "uroscopy" most often refers to routine uroscopy, and it is one of the most popular tests of routine examination. The test items included in routine uroscopy are visual inspection and biochemical tests, etc., wherein visual inspection refers to directly observation of the color and appearance of urine with naked eyes; biochemical tests refers to the urinary biochemical tests, which are often carried out with urine analyzer in hospital. The test items by urine analyzer are: urine protein, urine sugar, urine three bile pigments (urine bilirubin, urobilinogen and urobilin), urine volume, urine ketone, urobilinogen, urine specific gravity, and urine sediment. Compared with serum and other body fluid samples, the protein composition of urine is relatively simple, stable and easy to be analyzed, and can be used for the detection of many human diseases, especially diseases of urinary system. Therefore, regular urine examination is of great significance to detect urinary tract diseases.

2.2 Special urine examination

With the rapid development of molecular biology, the examination methods of urine changed from simplification to diversification. For example: 1. ELISA kits for detection of HIV antibodies in urine specimens, WB diagnostic kits for detection of HIV-1 antibodies in urine; 2. fluorescently labeled DNA probes for detection of the four kinds of chromosomal abnormalities associated with bladder cancer; 3. pregnancy test strip for detection of Human Chorionic Gonadotropin (hCG); 4. Streptococcus pneumonia antigen detection technique for screening of invasive pneumococcal infections; 5 K powder urine test board for detection of occult blood; 6 urine test kits for rapid detection of heroin.

Uroscopy is playing an increasingly important role in the clinical application, and more and more attention is being paid to it in product test and product R & D. Therefore, the study on urine has become a popular research direction, in which study on urine proteins is particularly prominent, including studies on specific proteins and whole proteomics.

3. Urinary proteomics

At the same time of proteomics study extensively extending into various fields of the medical community, urinary proteomics has also made great progress, and has achieved important research results in finding early diagnostic markers of various diseases of urinary tract and other systems and exploring the mechanisms of disease development.

3.1 Study status of normal urinary proteomics

In 1996, Marshall et al proposed the concept of urinary proteomics, which is to use the high-throughput of proteomics technologies and systematically to analyze and identify all proteins in urine and study their biological functions. They applied proteomics technologies to analyze the composition of normal urinary proteins for the first time. First, normal urine was condensed through dye precipitation, and then analysed by 2-dimensional electrophoresis (2-DE), but no protein was identified.

In 1997, Heine et al employed reversed phase chromatography (RP) and ion exchange chromatography to purify and separate peptides. Combining with high performance liquid chromatography-electrospray ionization-mass spectrometry (HPLC-ESI-MS), they analyzed the spectra of peptides and proteins of normal urine, and 34 high-abundance proteins were identified, including albumin, apolipoprotein, immunoglobulin, collagen, procollagen.

In 2001, Spahr et al identified 751 peptide sequence and 124 proteins using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Compared with 2-DE, LC-MS/MS is much quicker in analysis and identification, but it could not be used to quantitatively analyze the difference in protein content between different samples.

In 2002, Thongboonkerd et al analyzed normal adult urinary proteins isolated by acetone extraction and ultracentrifugation using 2-DE, discovered 67 spots by gel imaging, and identified 47 proteins by matrix assisted laser desorption ionization/time of flight mass spectrometry (MALDI-TOF-MS), including transport proteins, adhesion molecules, complement components, molecular chaperones, receptors, enzymes, matrix proteins, and signal-related proteins using MALDI-TOF-MS. The proteins and membrane proteins isolated by ultracentrifugation in this experiment can not be obtained by conventional acetone extraction, indicating that complete urinary protein mapping could not be obtained by using a single separation method.

In 2004, Pieper et al, by combining MALDI-TOF-MS with 2-D LC/ESI-MS/MS, separated nearly 140 protein spots and identified 150 unique urinary proteins, a third of which were classified as original plasma proteins in circulation. In 2004, Schaub et al analyzed normal urine using surface-enhanced laser-desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) and found that there were differences in protein composition for female midstream urine and first voided urine samples, while there were no such differences in male urine samples.

In 2004, Weissinger et al analyzed the urinary proteomes of 57 healthy volunteers, 16 patients with minimal change disease (MCD), 18 patients with membranous glomerulonephritis (MGN), and 10 patients with focal segmental glomerulosclerosis (FSGS) by capillary electrophoresis mass spectrometry (CE-MS). They identified 173 peptides with more than 90% probability, and 690 peptides with more than 50% probability from healthy individuals. Based on these data, they established a "normal" polypeptide pattern in healthy individuals. Peptides found in the urine of patients differed significantly from the normal controls. These differences allowed the distinction of specific protein spectra in patients with different primary renal diseases.

In 2004, Oh et al carried out proteomics analysis on the urine of 40 healthy adults (equal number of male and female) after precipitation trichloroacetic acid. In addition to some

potential-dependent protein spots, the urinary protein spots on 2-DE gel of male and female were almost identical (Figure 2), which can be used as standard 2-DE urinary protein profiles, providing a foundation for analyzing and looking for novel specific biomarkers for diseases in the future.

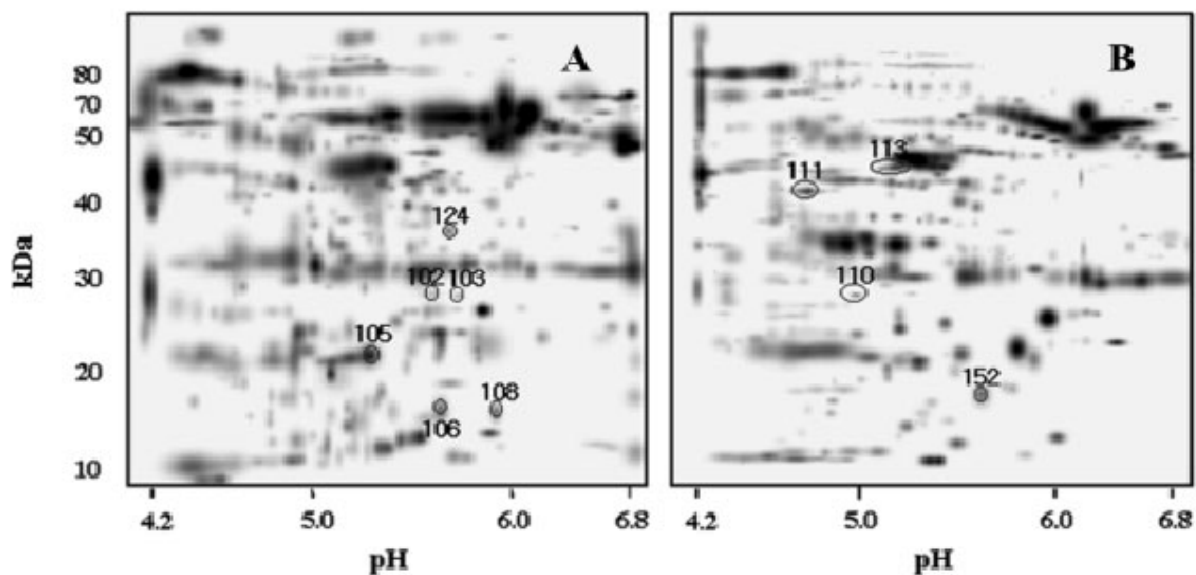


Fig. 2. Comparison of (A) female and (B) male urinary proteins separated on 2-D gels. Male and female specific proteins are indicated with circles (Oh et al,2004).

In 2005, Sun et al identified 226 special urinary proteins in combination 1-DE with 1-D LC/MS/MS, 1-D LC/MS/MS, or 2-D LC/MS/MS, and discussed the proteins identified by different methods. In 2005, Castagna et al confirmed 383 special gene products from urinary proteins enriched on coating beads with hexamer peptide ligand library in combination with linear ion trap-Fourier transform mass spectrometry (LTQ FTMS).

In 2006, Adachi et al employed 1-D sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and RP-HPLC for protein separation, and then used LTQ FTMS and LTQ Orbitrap-MS to analyze trypsin digested peptides. Finally, 1543 proteins and their fragments were identified in the urine of healthy individuals. Further research showed that most of the proteins in the urine were membrane proteins, which may derive from external secretion. In 2010, Li et al identified 1310 non-redundant high-confidence proteins using integrated multidimensional liquid chromatography (IMDL) and multidimensional liquid chromatography (MDLC).

In summary, good results have been achieved in normal urinary proteomics, the proteome profiles of healthy population have been gradually improved and supplemented. At the same time, the methods and techniques for urinary proteomics have also been further developed and optimized. However, the identification consistency of normal urine proteins by researchers is low, and the reliability of the results remains to be verified. The establishment of profiles of normal urinary proteomes plays an important role in screening different markers of urine differentiation for a variety of disease states.

3.2 Urinary proteomics technologies

The commonly used technologies for protein isolation and identification in urinary proteomics include SDS-PAGE, 2-DE, LC-MS, SELDI-TOF-MS, CE-MS (Figure 3, Figure 4). Currently, proteomics technologies have been extensively used in clinical diagnosis and various fields of biological study.

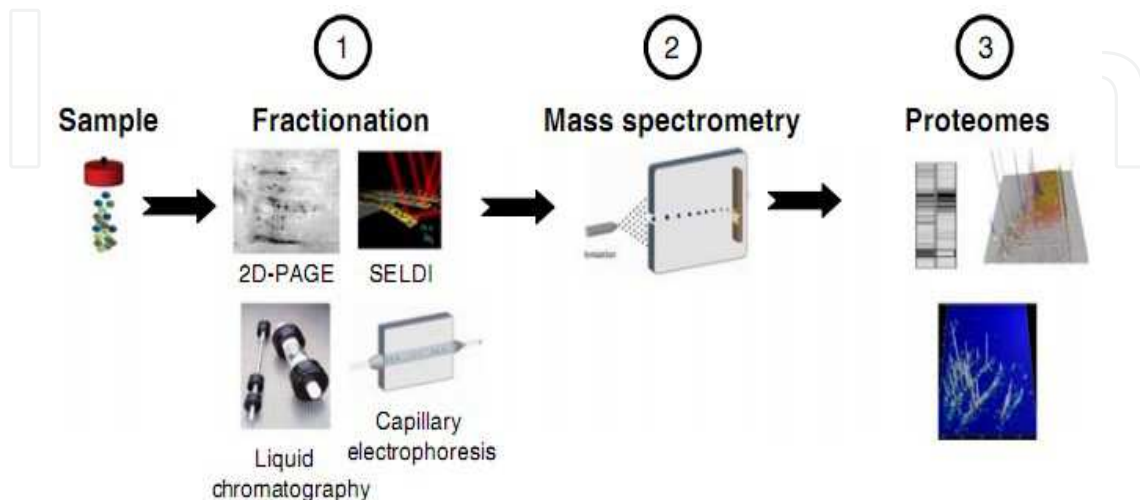


Fig. 3. Proteome analysis of urine requires fractionation to reduce complexity of the sample. 1 Fractionation can be obtained by different chromatographic techniques or by the specific absorption of a set of proteins on a surface. 2 These fractions are subsequently analyzed by MS where the relative abundance of the different proteins and peptides is determined. 3 Informatics treatment of the protein data in combination with the fractionation (example: migration time on a capillary or LC column) parameters yields protein profiles representing the (partial) protein content of samples. SELDI-TOF-MS, 2-D-PAGE (Caubet et al, 2010).

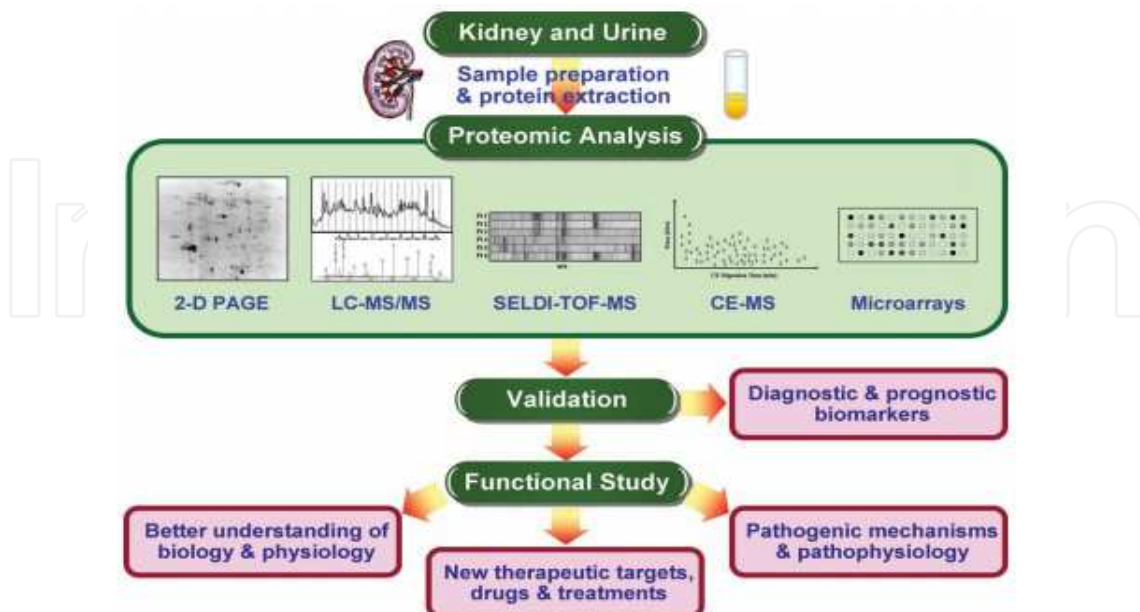


Fig. 4. Schematic summary of methodologies and applications of renal and urinary proteomics. 2-D PAGE; LC-MS/MS, SELDI-TOF-MS; CE-MS. (Thongboonkerd, 2010)

3.3 Significance and problems of urinary proteomics

Urinary proteomics related to the huge protein networks has exhibited widely application in many areas. The therapeutic intervention target molecules have demonstrated a valuable impact for the diagnosis and treatment technology, and have become a powerful weapon for clarifying the mechanisms, diagnosis, prevention and control of major human diseases. Although rapid developments have already been achieved in urinary proteomics technologies, some urgent problems still need to be solved, such as (1) the low amount of proteins in normal urine, imperfect enrichment techniques, and different urinary protein sample preparation methods, which can affect the isolation and identification of urinary proteins; (2) the determination of the best collection time of urine samples: the available studies have shown that urinary proteins in urine samples collected at different times show significant difference; (3) the elimination of various ions and high-abundance proteins without losing low-abundance proteins; (4) the analysis of extremely acidic, alkaline, small, large, low-abundance, and highly hydrophobic proteins using proteomics technologies; (5) the lack of adequate standard urine profiles for different diseases, and the further improvement of urinary protein data and bioinformatics; (6) the establishment of standard urine protein preparation and analytical methodology.

The broad prospects of urinary proteomics are beyond doubt, and urinary proteomics involves a large network of proteins, with the continuous development of science and technology of today, the above problems will gradually be resolved.

4. Urinary proteomics and diseases

With the development of front research in life sciences and the emergence of cutting-edge new technologies, proteomics has entered into a brand new era of studying functional proteomics in large scale and high-throughput, and could play an important role in the study of major diseases. Back in the late 1990s, people have begun to identify urinary proteins. The available studies have shown that survivin and cox2-2 proteins in urine are valuable for the diagnosis of early bladder cancer; transforming growth factors TGF- β 1 and laminin (LN) have some relevance to breast cancer; the detection of podocalyxin has a very important diagnostic value for early renal damage in diabetic patients; AQP-2 protein plays a key role in water metabolism disorder in patients with liver cirrhosis; AQP-2 has diagnostic value in hypertension. Studies on disease biomarkers are the most popular hotspot in urinary proteomics.

4.1 Developmental trend of urinary proteomics in renal diseases

As early as the 1990s, researchers have begun urinary proteomics in renal diseases, and have found some special diagnostic biomarkers and characteristic spectra. Compared with traditional methods, diagnostic specificity was greatly improved, and these methods were easily accepted by patients. In renal diseases, such as renal cancer, glomerular disease, acute renal transplantation rejection, researchers have already begun urine diagnostic biomarker related study. But no significant achievement and dramatic breakthrough were reported. Therefore, researchers need make more efforts to actively promote the progress of research in this area.

The identification of urinary proteomes shows great potential in diagnosis and monitoring of renal diseases, and is the important direction of developing non-invasive diagnosis and monitoring for renal diseases. Another important goal for proteomic research is to apply newly discovered biomarkers into clinical laboratory testing. This method is convenient, rapid, repeatable, and non-invasive. The entire process only takes 3 to 4 hours, greatly reducing the time for histopathologic examination, which makes great contribution to improve the post-operative care level after renal transplantation. Renal transplantation was the earliest developed and also the most mature organ transplantation currently, which provides a second life chance for patients with advanced renal failure. However, transplantation rejection is still an insurmountable obstacle in the field of transplantation.

4.2 Renal transplantation and acute rejection

Acute rejection (AR) is the most common form rejection in clinical. It can occur at any time after renal allograft transplantation, but mostly occurs in the 3 months after transplantation, while within the first month is the most common. AR is not only a vital factor to influence the long-term survival of the kidney transplanted, but also the major reason to cause the early graft damage, long-term graft dysfunction, and chronic graft nephropathy. Until now, to carry out transplantation renal biopsy and pathological histology is the only way to confirm definite diagnosis. However, these methods cause not only pain in patients but also a certain degree of renal damage. Furthermore, rejection is a continuous biological process occurred under the use of immunosuppressant, and the diagnosis by renal biopsy is only based on the tissue samples at a certain time. For some patients, immunological changes could not be observed in rejection even if a pathological examination has been carried out and it is difficult to differentiate from the damages caused by the use of immunosuppressant, and the diagnosis takes two to three days. Thus, it is urgently need a frequently used and non-invasive detection method for early detection of markers of allograft damages.

4.3 Acute renal allograft rejection status of proteomics

Clarke et al analyzed the urinary proteins from renal transplantation patients with AR (17 recipients) and without rejection (15 recipients) using SELDI-TOF-MS. Significant differences were observed at 6.5KD, 6.7 KD, 6.6 KD, 7.1 KD and 13.4 KD between the two groups, while 10.0 KD and 3.4 KD were found to have a sensitivity of 83% and a specificity of 100% in diagnosing AR. It was also found that several groups of proteins specifically appeared in the urine of AR patients, which are likely to serve as diagnostic markers of AR.

O'Riordan et al studied the urine of renal transplantation patients using SELDI-TOF-MS. 3 proteins with peak value at 4.7kDa, 25.6kDa and 19.0kDa, sensitivity between 90.5 % ~ 91.3% and specificity between 77.2 % ~ 83.3 %, were screened out, which could serve as important biomarkers for distinguishing of AR patients from stable renal function patients. For the follow-up study, two peptides, β -defensin -1 (4.7KD) and Alpha 1-antichymotrypsin (4.4KD), were indentified. Compared with patients with stable renal function after transplantation, β -defensin -1 decreased in the urine of AR patients while Alpha 1-antichymotrypsin increased ($P < 0.05$). The study showed that the ratio of β -defensin -1 and Alpha 1-antichymotrypsin in urine might be a potential new biomarker for diagnosing AR after renal transplantation.

To use SELDI-TOF-MS, Schaub et al found three peak clusters in 17 AR patients among 18 renal transplant patients, four out of 22 stable transplant patients, zero out of 28 control patients. The follow-up study showed that these peak clusters derived from non-trypsin attached from of urine β 2-micglobulin (β 2-m). Thus, β 2-m may be use as acute tubular injury biomarker, becoming one of the standards of non-invasive early AR diagnosis.

Reichelt et al analyzed the urine of 13 renal biopsy confirmed AR patients and 10 renal transplant patients without pathological symptom of rejection by using SELDI-TOF-MS, and two biomarkers, 25.71kDa and 28.13kDa, were found, the diagnostic sensitivity was 90% and 93% respectively, and the specificity was 80% and 85% respectively. SELDI-TOF-MS appears to be a promising new diagnostic tool for distinguishing renal transplant patients with AR from those without rejection or healthy volunteers.

Jia et al chose urine as the object to find biomarkers for AR using 2-DE-MS and Westernblot assay. They obtained 30 protein spots with significant decline trend by MS, and identified 16 protein spots. Among them, three proteins, alpha-1-antichymotrypsin, tumor rejection antigen gp96, and Zn-Alpha-2-Glycoprotein associated with immune rejection, which may be candidate biomarkers for early clinical diagnosis of AR after renal transplantation.

Freue et al studied the plasma proteome collected from 32 patients with and without renal biopsy confirmed AR after renal transplantation using iTRAQ-MALDI-TOF/TOF. They found that 18 plasma proteins to be related to inflammation could be potential plasma biomarkers. Plasma biomarkers may be used to monitor post-transplant and permit effectively therapeutic intervention to minimize graft damage.

A large number of studies showed that some special biomarkers found in the urine of patients with AR after renal transplantation had a certain degree of reproducibility. However, above mentioned studies still need to design reasonably to improve the sensitivity and specificity of the results so that these potential biomarkers could be used for clinical screening.

4.4 Proteomics in AR in renal transplantation and current problems

Renal transplantation is the main way to treat end-stage renal diseases. With the application of immunosuppressant, the survival rate for renal transplantation has been increased step by step. However, there is still rejection after renal transplantation. Currently, renal biopsy is still the main basis for diagnosis, but mostly biopsy is only carried out when symptoms occur to the patients, diagnosis can not be made in advance, and there are some risks for renal biopsy itself. The ideal way is to find some specific indicators in urine or blood to make diagnosis. The advantage of this kind of diagnosis is that it is non-invasive, and the change of some biological indicators in body fluid appeared earlier than clinical symptoms, so diagnosis can be made in advance by taking advantage of these indicators. Even if urinary proteomics can not completely replace renal biopsy to become a “golden standard”, it may still be used as an early screening tool so that renal biopsy will be minimized and unnecessary renal biopsy will be avoided. Taking into consideration of the high cost of protein analysis, the proteins identified in different laboratories still need to be further confirmed. Thus, the use of urinary proteins to monitor patients of renal transplantation is difficult to be carried out clinically within a short period of time.

5. Developmental direction of proteomics

With the rapid development of proteomics and its extensive application in many areas, proteomics technologies have been applied to a variety of life sciences. Proteomic research subjects include prokaryotic microorganisms, eukaryotic microorganisms, plant, animals, and human being, involving many important biological phenomena, such as signal transformation, cell differentiation, and protein folding. Therefore, the new research direction is the inexorable development trend of proteomics.

5.1 Quantitative proteomics

At present, life sciences have entered the post-genomic era. The research focuses have shifted from the discovery of genetic information to functional analysis, attempting to qualitatively and quantitatively study the full set of proteins of a certain biological sample expressed under specific conditions. It is a research hotspot in post-genomic era. With the continuous deepening of research and development of experimental techniques, quantitative proteomics has become hot research topics. The focus of quantitative proteomics is the accurate quantitation of the complex proteins from biological samples. For special proteomes, their physical and chemical properties are highly complicated because the dynamic range of protein expression is large. Thus high-throughput and high sensitivity experimental platform, represented by biological mass spectrometry, is the effective means and key technology for proteomics research.

The performance indicators of biological mass spectrometry, such as resolution, sensitivity, speed, accuracy, reproducibility, and dynamic range, have continuously improved as the development of proteomics. However, technological advances could not solve all the problems. Furthermore, complex steps are used from sample preparation to data analysis, which will introduce not ignorable system errors, and as well as seriously affect the accuracy of quantitative analysis. Currently, the analysis strategies of quantitative proteomics based on biological mass spectrometry are as follows: fluorescent two-dimensional difference gel electrophoresis (2-D DIGE), isotope coded affinity tagging (ICAT), isobaric tags for relative and absolute quantitation (iTRAQ), stable isotope labeling with amino acids in cell culture (SILAC), chemical labeling with amino acids, and comparison of the difference of peptide mass spectra. Quantitative methods include relative and absolute quantitation. Relative quantitative proteomics, also known as comparative proteomics, refers to the comparative analysis of relative changes of protein expression in cells, tissues or body fluids under different physiological and pathological conditions. Absolute quantitative proteomics is to determine the quantity or concentration of each protein in cells, tissues or body fluids. Absolute quantitation of proteins is a method to compare particular peptide elements of a sample against a spiked in isotopic labeled synthetic analogue.

Proteomics quantitative information can be used to understand the functions of proteins in interaction network. The analysis of the absolute amount of clinical biomarkers could help us determine the occurrence and development of diseases, and this provides practical guidance for the clinical diagnosis and treatment of diseases.

5.2 Phosphoproteomics

Recently, protein post-translational modification has gradually become one of research hotspots in proteomics. Protein phosphorylation is a reversible post-translational

modification which plays an important role in cell proliferation, cell differentiation, cell signal transduction, regulation, transcription and translation, protein complex formation, and protein degradation. Therefore, the identification of phosphorylated proteins is an important part of research on post-translational modification. However, it is difficult to use mass spectrometry to directly detect phosphorylated proteins because of their low abundance. To solve this problem and enhance the signal response of phosphorylated peptides/proteins in mass spectra, we need to enrich phosphorylated peptides/proteins. The widely used and newly established isolation and enrichment methods of phosphoproteomics mainly include: antibody enrichment, kinase-specific enrichment, affinity enrichment, chemical modification, multi-chromatography separation and enrichment.

Li et al identified 31 phosphorylated proteins and 51 specific peptides from normal urine using proteomics methods. The rapid development of quantitative phosphoproteomics methods and technologies has laid a solid foundation for the study of spatial and temporal dynamics of protein phosphorylation and better understanding of biological functional of regulatory networks. As an important part of proteomics research, quantitative phosphoproteomics will meet great challenges in technologies and methods because of the unique characteristics of phosphorylated proteins. Phosphoproteomics will become an important study direction in the future.

5.3 Glycoproteomics

Glycosylation is one of the most common and important post-translational modification of proteins. It is currently known that at least one half of mammal proteins are glycoprotein, which widely distributed in various cells and tissues, especially abundant in the cell surface and body fluids. Protein glycosylation has important biological functions, such as participation in cell adhesion and signal transformation, influence on the secretion and stability of proteins, elimination of the aging proteins in plasma, immune and inflammatory response, and recognition of egg and sperm. Protein glycosylation is of great significance in diseases, especially in the occurrence, development and metastasis of tumors. In a particular state, the amount of glycoprotein and /or the change of sugar chain structure of glycoprotein reflect the change of physiological or pathological states, such as the autoimmune diseases caused by sugar chain abnormality of immunoglobulin (Ig), rheumatoid arthritis, IgA nephropathy, thyroiditis, systemic lupus erythematosus, and AIDS.

In 2006, Wang et al identified 225 glycoprotein enriched by ConA lectin from the urine of normal young volunteers using LTQ. Currently the discovered biomarkers of a variety of known diseases are glycoprotein, such as prostate specific antigen which could serve as suggestive biomarker for prostate cancer, tumor antigen CA125 etc.

Hence, researches on glycoprotein have great biological significance and application prospect. Glycoproteomics has begun to attract more and more attention. In recent years, with the rapid development of proteomics technologies, glycoproteomics has also gained considerable progress. At current stage, researches on glycoproteome are mainly focused on the development and utilization of methodology. The existing enrichment methods, such as lectin affinity chromatography, solid phase capture based on chemical reaction, are relatively mature, and are currently the most widely applied methods for glycoprotein enrichment. Although the research methods of glycosylation sites have been improved

gradually, to solve the main problems existed still depends on the further development of mass spectrometry. We believe that, as the development of technologies, glycoproteome will play a greater role in further improvement of proteome expression, the discovery of biological markers in disease proteomics, and the research of drug targets.

6. Conclusion

For many patients with end-stage renal failure, renal transplantation is their first choice, the prognosis is good, but long-term survival rate has not yet achieved great improvement. Each patient should insist on taking immunosuppressant after renal transplantation, which is essential for the long-term prognosis of renal transplantation. Therefore, it is urgently needed for a non-invasive testing method to be used repeatedly for the early detection of biomarkers of allograft injury. Although current diagnostic methods have made some progress, none of them is absolutely reliable for clinical application. The combined application of many methods may lead to the increase of the diagnostic sensitivity and specificity. Its exact clinical application value needs to be further confirmed. In short, new diagnostic methods will continue to emerge as the development of technologies. Timely and accurate detection of AR through non-invasive or low-invasive methods is the future research direction. Although some progress has already made in this area, there is still no reliable, less invasive, and costless method that can be applied to clinical practice. Urinary proteomics technologies have the potential to reveal the complex pathophysiology, and are expected to become a powerful tool to solve this problem. Researches based on large scale samples are expected to provide proof for clinical application.

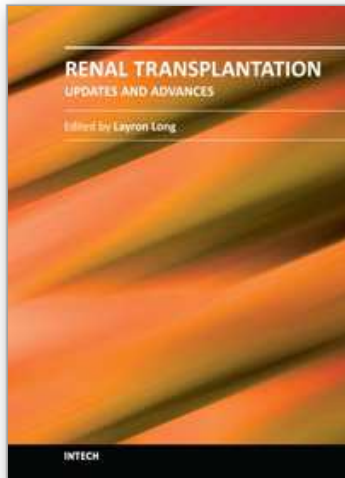
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