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Omics technology in diabetic kidney disease

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Abstract: Diabetic kidney disease (DKD) is a common complication of diabetes mellitus and one of the main causes of end-stage renal disease. Recent studies have shown that DKD has replaced primary glomerular disease as the leading cause of chronic kidney disease in China, and it is an increasingly serious global health problem. Understanding the development and progression of DKD is challenging due to the complexity and heterogeneity of kidney structure and function in healthy and pathological states. In recent years, omics technology has been more and more widely used in the study of DKD due to its advantages of high efficiency, speed and accuracy, and has made progress in the discovery of biomarkers, pathogenesis and early diagnosis of DKD. This article reviews the application of different omics techniques and multi-omics joint analysis in the development and progression of DKD, aiming to offer new ideas for the early diagnosis and guiding treatment of DKD.

Keywords: Diabetic kidney disease; Genomics; Transcriptomics; Proteomics; Metabolomics; Multi-omics study; Biomarker

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According to a survey report by the International Diabetes Federation, the prevalence of diabetes has risen significantly; in 2015, nearly 415 million people were affected, and it is projected to reach 642 million by 2040[1]. Diabetic kidney disease (DKD) is one of the major microvascular complications of diabetes and has become a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD)[2-3], markedly increasing the risk of cardiovascular events and mortality. Patients with DKD often lack obvious clinical symptoms in the early stage; however, once diagnosed, significant and irreversible damage has already occurred to the body. Currently, the diagnosis of DKD relies on laboratory indices, including persistent proteinuria and a progressive decline in glomerular filtration rate (GFR)[4-5]. However, studies have shown that some DKD patients present with normal albuminuria despite developing glomerular filtration dysfunction and declining GFR[6]. The gold standard for the diagnosis of DKD remains kidney pathological biopsy[7], but this is an invasive procedure that carries potential risks, such as bleeding, renal impairment, and even death. Due to these risks, kidney biopsies have not been widely implemented and are not suitable for monitoring therapeutic responses. Early identification and diagnosis of DKD at the subclinical stage can prevent or even halt disease progression, thereby reducing the risk of renal damage. In recent years, omics technologies have offered a high-throughput screening approach for efficiently and rapidly revealing detailed biological information about human diseases. Common omics technologies include genomics, transcriptomics, proteomics, metabolomics, single-cell omics, and spatial transcriptomics[8]. Different types of omics data can provide disease-related molecules with differential expression, which may serve as biomarkers during disease progression and help elucidate biological pathways or processes that differ between disease and control groups. Omics technologies allow for a more comprehensive understanding of biomarker screening, the elucidation of pathogenic molecular mechanisms, and the discovery of drug targets in DKD research.

At present, numerous studies have reported the characteristic changes during the development of DKD identified via various omics techniques; however, most reviews only summarize the advances in DKD research using a single omics approach. This article provides an overview of the application of genomics, transcriptomics, proteomics, metabolomics, and integrated multi-omics in DKD, aiming to offer new perspectives for the early diagnosis, early treatment, and precision therapy of DKD.

1 Genomics

Genomics is the foundation of omics technologies; it involves the application of omics to the entire genome, aiming to collect and quantify the features of all genes within an organism, reveal their interrelationships and effects on the organism, and thus to identify sequence variations in the human genome[9]. By investigating the association between genes/genomes and diseases, pathogenic loci and differentially expressed genes related to DKD can be identified. In 2004, Maeda[10] reported several novel pathogenic loci for DKD, such as *SLC12A3* and *ELMO1*, but further validation is needed. In addition, one study downloaded DKD gene chip data from the public Gene Expression Omnibus (GEO) database and used genomic analysis techniques to deeply mine and analyze glomerular gene chip data from DKD patients. The study indicated that the gene expression profile of glomeruli in DKD patients was significantly altered; compared to healthy individuals, 844 differentially expressed genes were found

in the glomeruli of DKD patients, mainly associated with inflammatory and stress responses[11].

Rapid advances in genomics have enabled the identification of novel susceptibility genes and biological pathways associated with disease, thereby opening new vistas for the diagnosis and treatment of DKD. However, the large volume of data generated by genomics is prone to statistical bias during analysis, and most of the identified genetic variants lack direct biological relevance to disease. Research conducted solely at the genomic level cannot comprehensively explain the dynamic regulation of disease development by the internal environment of the patient.

2 Transcriptomics

Transcriptomics refers to the study of the expression of all RNAs in a specific cell population and investigates the global molecular dynamics induced by environmental factors or pathogens[12]. As a complement to genomics, detecting changes in transcripts or the transcriptome at the molecular level is of great significance for DKD research. Currently, transcriptomics has been utilized for the identification of DKD biomarkers and the exploration of pathophysiological mechanisms. Hodgin *et al*.[13] performed transcriptomic studies using renal biopsy samples and found significant increases in Janus kinase, signal transducer and activator of transcription, vascular endothelial growth factor receptor-2, and hypoxia-inducible factor-1 in DKD patients. To elucidate pathomechanistic pathways differentially regulated in early DKD, Wu *et al.*[14] carried out transcriptomic analysis on glomerular endothelial cells isolated from neuronal nitric oxide synthase 3 gene knockout diabetic mice, and found that G-protein coupled receptor 56 (*GPR56*), also known as *ADGRG1*, was upregulated in DKD and negatively correlated with renal function. *GPR56* was shown to promote DKD progression by exacerbating glomerular endothelial injury and dysfunction.

Transcriptomics is an important approach to gaining biomarkers and discovering the interplay between genetic and environmental factors in disease. However, due to the huge data volume and the complexity of changes from microRNA levels to downstream protein function, identification of precise molecular targets remains challenging. Moreover, its suitability for real clinical settings and the feasibility of conducting independent cohort studies to assess biomarker performance require further investigation.

3 Proteomics

Proteomics enables the large-scale identification and quantification of all proteins in cells or tissues[15]. Since gene transcription levels are often affected by post-transcriptional modifications, RNA analyses usually lack correlation with protein expression[16]. Therefore, proteomics can directly quantify protein expression and provide information directly relevant to environmental changes or disease progression. Proteomics has been applied in biomarker discovery, evaluation of intervention efficacy, and drug safety assessment[17]. Darmayanti *et al*.[18] used liquid chromatography–tandem mass spectrometry (LC-MS/MS) to perform comparative urinary proteomic analyses between type 2 diabetes patients and controls, showing that the abundance of vacuolar proton ATPase subunit C1 was significantly negatively correlated with microalbumin and strongly reduced in urine, whereas IKBIP (IκB kinase β-interacting protein) was upregulated and positively correlated with microalbumin. Levels of these proteins differed significantly among the control, type 2 diabetes, and DKD groups, indicating their association with DKD progression and potential as preliminary biomarkers for DKD risk prediction. Li *et al*.[19] employed ultra-sensitive quantitative phosphoproteomics to identify phosphoproteins in urinary extracellular vesicles as potential biomarkers for DKD. Compared with diabetic patients, 47 phosphoproteins were significantly altered in DKD patients, suggesting that phosphorylation changes in urinary extracellular vesicles reflect corresponding alterations in the kidney and have potential as candidate DKD biomarkers and as a feasible diagnostic tool for kidney disease. Fan *et al.*[20] uncovered alterations in the DKD proteomic profile and identified vimentin and β2-microglobulin as early biomarkers of DKD, laying the groundwork for its prevention, diagnosis, and treatment, although their underlying mechanisms warrant further exploration. Peng *et al.*[21] used quantitative proteomics and Mfuzz clustering analysis on serum samples from healthy controls, diabetes patients, early/intermediate DKD, and advanced DKD patients. They found that 15 proteins increased during DKD progression, including high mobility group box 1 (HMGB1), which emerged as a promising biomarker closely associated with renal function changes, indicating potential as an early DKD biomarker and early monitoring target. This study advanced the understanding of DKD and set the stage for future clinical diagnostic application.

Proteomics has also attracted much attention in predicting treatment efficacy and elucidating drug mechanisms. Proteomics has broadened our understanding of DKD pathophysiology and early/prognostic biomarkers but faces several challenges. These novel biomarkers require further verification and clinical translation, necessitating the design and implementation of large-scale validation studies.

4 Metabolomics

Metabolomics is a modern strategy focusing on small-molecule endogenous metabolic products, including substrates, intermediates, and final products of cellular metabolism, such as carbohydrates, fatty acids, and amino acids[22]. Depending on the research aims or subjects, metabolomics can be divided into untargeted and targeted approaches. The most commonly used platforms are nuclear magnetic resonance and LC-MS[23]. Unlike genomics or proteomics, which emphasize genetic or protein expression outputs, metabolomics provides a direct snapshot of the physiological state at any given moment[24]. Metabolomics plays a crucial role in the discovery of biomarkers for early prediction, early diagnosis, and disease progression in DKD. Feng *et al*.[25] divided 95 diabetic patients into simple

diabetes mellitus (SDM), albuminuria DKD (ADKD), and normoalbuminuric DKD (NADKD) groups. Using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS)-based untargeted urinary metabolomics, they found significant differences in urinary metabolomic profiles among the SDM, NADKD, and ADKD groups. ADKD patients showed distinct levels of linoleic acid metabolism-, citric acid cycle-, arginine- and proline metabolism-related metabolites compared to SDM and NADKD patients. However, these metabolites did not differ significantly between SDM and NADKD groups, offering insights for understanding the NADKD pathogenesis and biomarker screening. Xu *et al*.[26] used UPLC-MS-based metabolomics combined with pattern recognition to identify 19 differentially expressed endogenous metabolites associated with DKD, providing a direction for further research. Ma *et al.*[27] performed UPLC-MS-based untargeted metabolomic analysis of DKD patient urine, identifying 147 metabolites and five DKD-pathophysiology related pathways. Altered pantothenate and Coenzyme A biosynthesis were most significant in DKD patients. The study indicated that pantothenate may serve as a novel predictive biomarker for DKD occurrence and progression. Moreover, these findings suggest that the pantothenate and CoA biosynthesis pathways may be promising therapeutic targets for DKD. Mogos *et al*.[28] performed comprehensive metabolomics analysis on blood and urine samples from 90 type 2 diabetes patients using UHPLC-QTOF-ESI* MS, identifying urinary O-phosphoserine, aspartate, 5-hydroxylysine, uric acid, and methoxytryptophan as metabolites distinguishing healthy controls, DKD, and different proteinuria subgroups. Identification of these potential biomarkers indicate their roles in early DKD and type 2 diabetes progression, but further targeted longitudinal metabolomics studies are required to validate these findings.Mogos *et al*.[28] also reported that serum glycine and kynurenic acid, and urinary tryptophan and tiglylglycine may serve as early biomarkers for DKD, but further research is needed for validation.

Metabolomics can reflect physiological or pathological states of the organism, but the results may be affected by age, sex, diet, disease state, environmental changes, or therapeutic interventions. In addition, due to small sample sizes, result heterogeneity, and lack of integrative validation, most DKD biomarkers remain unidentified and systematic work for biomarker validation and clinical evaluation is limited. Nonetheless, the potential benefits of metabolomics in DKD research are substantial despite these challenges.

5 Multi-Omics

In practical research, a single omics approach can only assess disease correlation, primarily reflecting disease-associated changes without explaining causality. Multi-omics generally refers to the integrative application of several high-throughput screening techniques—represented by genomics, transcriptomics, single-cell omics, proteomics, and metabolomics—to advance research in human disease. Integration of disparate omics datasets can illuminate potential pathogenic changes, which can then be validated in further molecular studies. Through multi-omics integration, novel associations between biomolecules and disease phenotype can be filtered, relevant signaling pathways can be identified, and comprehensive disease biomarkers can be established, while simultaneously revealing potential therapeutic targets in DKD. Multi-omics holds the promise of providing unprecedented insights into DKD mechanisms and the discovery of potential biomarkers. Jiang *et al.*[29] integrated metabolomics and peptidomics to investigate biological changes in DKD pathogenesis and found that 10 metabolites and 6 polypeptides are sequentially regulated at different DKD stages, significantly improving the accuracy of early DKD diagnosis and status discrimination. Yang *et al.*[30], using human glomerular endothelial cells as a cellular model and applying UPLC-MS-based metabolomics and tandem mass tag-based proteomics, suggested that serum exosomes extracted from DKD patients may induce endothelial dysfunction primarily by upregulating coagulation factor fibrinogen alpha chain and downregulating 1-methylhistidine. Liu *et al.*[31] conducted integrative proteomic and large-scale metabolomic analysis on serum samples, improving stability and accuracy in distinguishing DKD statuses and providing reliable biomarkers for early warning and diagnosis. Zhao *et al.*[32] performed integrated transcriptomic and proteomic analysis of glomerular samples from 50 biopsy-confirmed DKD patients and 25 controls, revealing for the first time that selective alternative polyadenylation and 3`UTR lengthening contribute to DKD progression by enhancing translation of corresponding proteins, offering new mechanistic insights. Wei *et al.*[33] applied LC-MS and next-generation sequencing, as well as tandem mass tag labelling, to evaluate mRNA, protein, and phosphosite changes between DKD and model mice, revealing RAS, RAP1, AMPK, PPAR, and HIF-1 signaling pathways as critical in DKD pathogenesis. This approach suggests that targeting specific molecules, proteins, kinases, and key pathways may be a promising therapeutic strategy for DKD. Sharma *et al.*[34], using a multi-omics approach, identified the metabolite adenine as a noninvasive biomarker of early DKD progression; through spatial metabolomics, single-cell transcriptomics, and experimental work, they showed that the mechanistic target of rapamycin (mTOR) pathway is involved in adenine-induced tissue fibrosis, demonstrating the potential of multi-omics to elucidate DKD mechanisms and targeted therapies.

Integration of multi-omics enables multi-system, multi-level, multi-dimensional, and multi-angle elucidation of disease development, characterization, and comprehensive understanding, with great potential. However, significant challenges remain, including the complexity of inter-omics regulatory mechanisms, data integration, high detection costs, and limited large-scale clinical application.

6 Summary and Outlook

DKD increases mortality in diabetic patients and has become a major global health challenge. The pathogenesis of DKD is complex and involves intricate regulatory networks; it cannot be adequately investigated in isolated

segments but should, instead, be explored from a multi-dimensional, multi-angle systemic biology perspective. Typical progression of DKD is characterized by proteinuria and reduced glomerular filtration rate; however, reliance on these clinical indicators for DKD diagnosis has limitations, and there is an urgent clinical need for more sensitive, accurate biomarkers for early diagnosis and progression assessment. Ideal biomarkers should possess high sensitivity, specificity, non-invasiveness, ease of acquisition, and stability.

Emerging technologies such as omics and high-throughput screening offer more avenues for the identification of ideal DKD biomarkers. Single-omics technologies alone cannot fully realize their potential in disease research; integration of different omics datasets will help elucidate underlying pathogenic variations and facilitate further validation in molecular studies. With the ongoing development of multi-omics, novel associations between biomolecules and disease phenotypes can be filtered, relevant signaling pathways can be identified, and detailed disease biomarkers can be constructed. This holds significant implications for early diagnosis, therapeutic monitoring, and prognosis assessment of DKD, and also provides new clues for mechanistic research and therapeutic target identification. Ultimately, these advances will contribute to the realization of individualized, targeted precision medicine.

Conflict of interest None

Reference

[1] Yu MG, Gordin D, Fu JL, et al. Protective factors and the pathogenesis of complications in diabetes[J]. Endocr Rev, 2024, 45(2): 227-252.
[2] Wang N, Zhang C. Recent advances in the management of diabetic kidney disease: slowing progression[J]. Int J Mol Sci, 2024, 25(6): 3086.
[3] Büttner F, Barbosa CV, Lang H, et al. Treatment of diabetic kidney disease. A network meta-analysis[J]. PLoS One, 2023, 18(11): e0293183.
[4] Chen YQ, Wang NS. Current status of diagnosis and treatment of diabetic nephropathy[J]. Chin J Clin, 2020, 48(5): 508-511.**[In Chinese]**
[5] Wu L, Zhao YY, Li MR, et al. Clinical and pathological characteristics of DKD patients with early-onset type 2 diabetes[J]. J Diabetes Complications, 2023, 37(8): 108520.
[6] Microvascular Complications Group of Chinese Diabetes Society. Clinical guideline for the prevention and treatment of diabetic kidney disease in China (2021 edition) [J]. Chin J Diabetes Mellitus, 2021, 13(8): 762-784. **[In Chinese]**
[7] Cheng L, Fu P. Diagnosis and differential diagnosis of diabetic kidney disease: renal biopsy in diagnosis of diabetic kidney disease[J]. Chin J Pract Intern Med, 2017, 37(3): 192-194. **[In Chinese]**
[8] Vandereyken K, Sifrim A, Thienpont B, et al. Methods and applications for single-cell and spatial multi-omics[J]. Nat Rev Genet, 2023, 24(8): 494-515.
[9] Prokop JW, May T, Strong K, et al. Genome sequencing in the clinic: the past, present, and future of genomic medicine[J]. Physiol Genomics, 2018, 50(8): 563-579.
[10] Maeda S. Genome-wide search for susceptibility gene to diabetic nephropathy by gene-based SNP[J]. Diabetes Res Clin Pract, 2004, 66(Suppl 1): S45-S47.
[11] Ren XM, Yang JF, Liu QL, et al. Mechanism of diabetic kidney disease and its relationship with cardiovascular disease based on genomics[J]. J Xi'an Jiaotong Univ Med Sci, 2018, 39(2): 266-270. [**In Chinese]**
[12] Costa V, Angelini C, De Feis I, et al. Uncovering the complexity of transcriptomes with RNA-seq[J]. J Biomed Biotechnol, 2010, 2010: 853916.
[13] Hodgin JB, Nair V, Zhang HY, et al. Identification of cross-species shared transcriptional networks of diabetic nephropathy in human and mouse glomeruli[J]. Diabetes, 2013, 62(1): 299-308.
[14] Wu JS, Wang ZH, Cai MC, et al. GPR56 promotes diabetic kidney disease through ENOS regulation in glomerular endothelial cells[J]. Diabetes, 2023, 72(11): 1652-1663.
[15] Chen L, Su W, Chen H, et al. Proteomics for biomarker identification and clinical application in kidney disease[J]. Adv Clin Chem, 2018, 85: 91-113.
[16] Pino L, Banarjee R, Basisty N. A bright future for proteomics of health and disease. Introduction to the US HUPO 2021 themed issue-proteomics from single cell to systems biology in health and disease[J]. Mol Omics, 2022, 18(10): 894-895.
[17] Deng L, Wang SQ, Li CC, et al. Progress in the use of proteomics in the diagnosis and treatment of diabetic nephropathy[J]. Health Med Res Pract, 2022, 19(9): 171-176. **[In Chinese]**
[18] Darmayanti S, Lesmana R, Meiliana A, et al. V-ATPase subunit C1 and IKBIP as tandem prospective biomarkers for diabetic nephropathy[J]. Diabetes Res Clin Pract, 2023, 203: 110887.
[19] Li Q, Zhang J, Fang Y, et al. Phosphoproteome profiling of uEVs Reveals p-AQP2 and p-GSK3β as potential markers for diabetic nephropathy[J]. Molecules, 2023, 28(14): 5605.
[20] Fan XE, Xu MH, Chen X, et al. Proteomic profiling and correlations with clinical features reveal biomarkers indicative of diabetic retinopathy with diabetic kidney disease[J]. Front Endocrinol, 2022, 13: 1001391.
[21] Peng R, Zuo SY, Li X, et al. Investigating HMGB1 as a potential serum biomarker for early diabetic nephropathy monitoring by quantitative proteomics[J]. iScience, 2024, 27(2): 108834.
[22] Zhang Q, Song W, Liang XC. Metabolomics in diabetic neuropathy[J]. Acta Acad Med Sin, 2022, 44(2): 313-317. **[In Chinese]**
[23] Zhang Q. A metabolic insight into the neuroprotective effect of Jin-Mai-Tong on diabetic rats with peripheral neuropathy based on metabolomics[D]. Beijing: Peking Union Medical College, 2020. **[In Chinese]**
[24] Luo YY, Zhang W, Qin GJ. Metabolomics in diabetic nephropathy: Unveiling novel biomarkers for diagnosis (Review)[J]. Mol Med Rep, 2024, 30(3): 156.
[25] Feng Q, Li YM, Yang YW, et al. Urine metabolomics analysis in patients with normoalbuminuric diabetic kidney disease[J]. Front Physiol, 2020, 11: 578799.
[26] Xu JN, Yuan Q, Wu K, et al. Effects of Bailing capsule on diabetic nephropathy based on UPLC-MS urine metabolomics[J]. RSC Adv, 2019, 9(62): 35969-35975.
[27] Ma T, Liu TH, Xie PF, et al. UPLC-MS-based urine nontargeted metabolic profiling identifies dysregulation of pantothenate and CoA biosynthesis pathway in diabetic kidney disease[J]. Life Sci, 2020, 258: 118160.
[28] Mogos M, Socaciu C, Socaciu AI, et al. Metabolomic investigation of blood and urinary amino acids and derivatives in patients with type 2 diabetes mellitus and early diabetic kidney disease[J]. Biomedicines, 2023, 11(6): 1527.
[29] Jiang XR, Liu XY, Qu XT, et al. Integration of metabolomics and peptidomics reveals distinct molecular landscape of human diabetic kidney disease[J]. Theranostics, 2023, 13(10): 3188-3203.
[30] Yang J, Liu DW, Liu ZS. Integration of metabolomics and proteomics in exploring the endothelial dysfunction mechanism induced by serum exosomes from diabetic retinopathy and diabetic nephropathy patients[J]. Front Endocrinol, 2022, 13: 830466.
[31] Liu SJ, Gui Y, Wang MS, et al. Serum integrative omics reveals the landscape of human diabetic kidney disease[J]. Mol Metab, 2021, 54: 101367.
[32] Zhao TT, Zhan DD, Qu S, et al. Transcriptomics-proteomics Integration reveals alternative polyadenylation driving inflammation-related protein translation in patients with diabetic nephropathy[J]. J Transl Med, 2023, 21(1): 86.
[33] Wei L, Gao JJ, Wang LZ, et al. Multi-omics analysis reveals the potential pathogenesis and therapeutic targets of diabetic kidney disease[J]. Hum Mol Genet, 2024, 33(2): 122-137.
[34] Sharma K, Zhang G, Hansen J, et al. Endogenous adenine mediates kidney injury in diabetic models and predicts diabetic kidney disease in patients[J]. J Clin Invest, 2023, 133(20):e170341.

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·研究进展·

组学技术在糖尿病肾病中的应用

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摘要：糖尿病肾病（DKD）是一种糖尿病常见并发症，是导致终末期肾病的主要原因之一。研究显示，DKD已经取代原发性肾小球疾病成为我国慢性肾脏病的首位病因，成为了一个日益严重的全球性健康问题。肾脏健康和病变状态下结构和功能的复杂性和异质性使得理解DKD的发生和发展具有挑战性。近年来，组学技术由于其高效、快速、准确等优点，已经越来越广泛地应用于DKD的研究，在DKD生物标志物的发现、发病机制的探索和早期诊断等方面均取得进展。本文就不同组学技术及多组学联合分析在DKD发生发展中的应用作一概述，旨在为DKD的早期诊断和指导治疗提供新的思路。

关键词：糖尿病肾病；基因组学；转录组学；蛋白质组学；代谢组学；多组学研究；生物标志物

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Abstract：Diabetic kidney disease（DKD）is a common complication of diabetes mellitus and one of the main causes of end-stage renal disease. Recent studies have shown that DKD has replaced primary glomerular disease as the leading cause of chronic kidney disease in China，and it is an increasingly serious global health problem. Understanding the development and progression of DKD is challenging due to the complexity and heterogeneity of kidney structure and function in healthy and pathological states. In recent years，omics technology has been more and more widely used in the study of DKD due to its advantages of high efficiency，speed and accuracy，and has made progress in the discovery of biomarkers，exploration of pathogenesis and early diagnosis of DKD. This article reviews the application of different omics techniques and multi-omics joint analysis in the development and progression of DKD，aiming to offer new insights for the early diagnosis and treatment guidance of DKD.

Keywords：Diabetic kidney disease；Genomics；Transcriptomics；Proteomics；Metabolomics；Multi-omics study；Biomarker

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国际糖尿病联合会调查报告显示，糖尿病的患病率显著上升，2015年有近4.15亿人受到影响，预计到2040年将达到6.42亿[1]。糖尿病肾病（diabetic kidney disease，DKD）是糖尿病的主要微血管并发症之一，已成为慢性肾脏病（chronic kidney disease，CKD）和终末期肾病（end-stage renal disease，ESRD）的主要原因[2-3]，并显著增加了心血管事件和死亡风险。DKD患者早期无明显临床症状，而一旦确诊，其对机体已经造成了严重损害，且病情无法逆转。目前，DKD的诊断大多依赖于实验室指标，包括持续存在的蛋白尿和肾小球滤过率进行性降低[4-5]。但有研究表明，部分DKD患者尽管出现肾小球滤过功能障碍，肾小球滤过率下降，但仍表现为正常白蛋白尿[6]。诊断DKD的金标准仍然是肾脏病理活检[7]，但这是一种具有潜在风险的侵入性检查，会导致出血、肾损害，甚至死亡，这种侵入性检查尚未广泛实施，也不适合监测治疗反应。而在亚临床阶段早期识别和诊断DKD可以预防甚至阻止疾病进展，有利于降低肾损伤风险。近年来，组学技术为高效、快速地揭示人类疾病的详细生物学信息提供了一种高通量筛选方法。常见的组学技术包括基因组学、转录组学、蛋白质组学、代谢组学、单细胞组学、空间转录组学等[8]。不同类型的组学数据可以提供差异表达的疾病相关分子，这些分子可以在疾病进展期作为生物标志物，并帮助了解疾病组和对照组之间有哪些生物学途径或过程不同。组学技术使研究者对DKD筛选

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生物标志物、揭示致病分子机制、发现药物作用靶点等研究中有了更全面的认识。

目前，已有大量文献报道了通过不同的组学技术对DKD发生发展过程中特征性改变的研究结果，但大多数综述只对单一组学技术在DKD中的研究进展进行总结，本文就基因组学、转录组学、蛋白质组学、代谢组学，以及整合多组学在DKD中的应用进行概述，旨在为DKD的早诊早治及精准治疗提供新的思路。

1　基因组学

基因组学是组学技术的根基，是组学在全基因组中的应用，旨在收集和量化生物体所有基因的特征，揭示它们之间的相互关系和对生物体的影响，从而发现整个人类基因组中存在的序列变异[9]。通过研究基因和基因组与疾病之间的关系，可以识别与DKD相关的致病基因位点及差异表达基因。2004年Maeda[10]报道了多个新的DKD致病基因位点，如*SLC*12A3、*ELMO*1等，但有待进一步验证。此外，一项研究从基因芯片公共数据库（Gene Expression Omnibus，GEO）中下载了DKD基因芯片数据，利用基因组学分析技术，对DKD患者肾小球组织基因芯片检测数据进行了细致挖掘和分析，研究表明，DKD患者肾小球组织的基因表达谱有明显改变，与健康人群相比，DKD患者肾小球组织有844个差异表达基因，且这些差异表达基因主要与炎症反应、应激反应相关[11]。

基因组学研究迅速发展，可以识别新疾病的相关易感基因和生物学途径，为DKD的诊疗开辟了新的视野，但基因组学产生的大量数据在进行统计分析时极易造成偏倚，而且大多数获得变异的基因与疾病没有直接的生物学相关性。单从基因组学水平进行研究，较难全面地阐释患者体内环境对疾病发展动态调控的过程。

2　转录组学

转录组学是指研究特定细胞群体中所有RNA的表达，从全局角度研究环境因素或病原体诱导的分子动力学变化[12]。作为基因组学的补充，从分子层面检测转录本或转录组的改变对DKD的研究有很大意义。目前，转录组学已应用于确定DKD生物标志物、探索病理生理机制等。Hodgin等[13]采用肾穿刺活检组织进行转录组学研究，发现Janus激酶、信号转导及转录激活因子、血管内皮生长因子受体-2、缺氧诱导因子-1等在DKD患者中明显升高。Wu等[14]为了揭示早期DKD中差异调节可能导致疾病发病机制的途径，对糖尿病一氧化氮合酶（neuronal oxide synthase，*NOS*）3基因敲除小鼠分离的肾小球内皮细胞进行了转录组学分析，发现其中一种编码基因——黏附G蛋白偶联受体（G-protein coupled receptor，*GPR*）56，也称为*ADGRG*1，在DKD中表达增强，且与肾功能呈负相关，*GPR*56通过增强肾小球内皮损伤和功能障碍来促进DKD进展。

转录组学是获取疾病生物标志物、发现疾病遗传和环境因素相互作用规律的重要手段。但由于转录组数据量庞大，且从微小RNA水平至下游蛋白质功能的改变极为复杂，因此对分子靶点的探寻仍充满挑战。而且其是否适合真实临床应用环境，能否开展独立队列研究及评估相关生物标志物性能还有待进一步研究。

3　蛋白质组学

蛋白质组学能够最大限度地鉴定和定量细胞或组织中的所有蛋白质[15]。由于基因转录水平经常受到转录后修饰的影响，RNA分析通常缺乏与蛋白质表达的相关性[16]。因此，蛋白质组学可以量化蛋白质的表达，并提供与环境变化或疾病进展直接相关的信息。蛋白质组学已应用于发现生物标志物、评估干预效果、评估药物安全性等方面[17]。Darmayanti等[18]采用液相色谱（liquid chromatography，LC）串联质谱（mass spectrometry，MS）联用技术比较2型糖尿病患者和对照组的尿液蛋白质组学分析，表明液泡质子ATP酶亚基C_1丰度与微量白蛋白呈显著负相关，在尿液中显著降低，而*IKBIP*编码的IκB激酶β相互作用蛋白表达升高与微量白蛋白呈正相关，这些蛋白质的水平在对照组、2型糖尿病组和DKD组之间显著不同，这意味着它们与DKD的进展有关，可作为初步诊断DKD时预测风险的生物标志物。Li等[19]使用超高灵敏度的定量磷酸化蛋白质组学鉴定尿细胞外囊泡中的磷酸蛋白作为DKD的潜在生物标志物，与糖尿病患者相比，DKD患者中有47个磷酸蛋白表现出显著的改变，表明尿细胞外囊泡中磷酸化蛋白的改变反映了肾脏内相应的变化，并具有作为DKD候选生物标志物的潜力，且有潜力成为肾脏疾病的高度可行的诊断工具。Fan等[20]揭示了DKD蛋白质组学谱的改变，并确定波形蛋白和β2微球蛋白是DKD的早期生物标志物，为DKD的预防、诊断和治疗奠定了基础，但其作用机制仍需进一步探索。Peng等[21]使用来自健康对照、糖尿病、早/中期DKD和晚期DKD的血清样本，采用定量蛋白质组学和Mfuzz聚类分析，结果显示，15种蛋白质在DKD进展过程中表达增加，其中高迁移率族蛋白B1（high mobility group box1，HMGB1）成为一种很有前途的生物标志物，与肾功能变化密切相关，具有DKD早期检测生物标志物的潜力，是一种有前途的早期监测靶点。该研究促进了对DKD的理解，为DKD的未来临床诊断应用奠定了基础。

蛋白质组学在预测疾病治疗效果、分析药物机制等方面同样获得很多关注。蛋白组学研究的结果提高了对DKD病理生理、早期和预测DKD进展的生物标志物的认识，但仍然面临着诸多挑战，这些新型标志物尚未经过验证及临床应用，需要通过开发不同研究设计并实施大规模验证性研究。

4　代谢组学

代谢组学是一种专注于小分子内源性代谢产物的现代策略，这些代谢物包括细胞代谢的小分子底物、中间体和最终产物，如碳水化合物、脂肪酸和氨基酸等[22]。根据研究目的或对象的不同，代谢组学分为非靶向和靶向代谢组学，最常用的技术平台包括核磁共振和LC-MS两种[23]。与基因组学或蛋白质组学相反，前者侧重于遗传或蛋白质表达的输出，代谢组学则

提供了在任何给定时刻的生理状态的直接视图[24]。代谢组学在DKD早期预测、早期诊断、疾病进展等生物标志物的筛选中发挥重要作用。Feng等[25]将95例糖尿病患者分为单纯糖尿病(simple diabetes mellitus,SDM)组、白蛋白尿糖尿病肾病(albuminuria diabetic kidney disease,ADKD)组和正常白蛋白尿糖尿病肾病(normoalbuminuric diabetic kidney disease,NADKD)组,使用基于超高效液相色谱(ultra-performance liquid chromatography,UPLC)串联MS的非靶向代谢组学分析尿液代谢物,发现SDM组、NADKD组和ADKD组的尿液代谢组学特征存在显著差异,ADKD组患者在与亚油酸代谢、柠檬酸循环、精氨酸和脯氨酸代谢相关的代谢物水平上与SDM组和NADKD组患者差异显著。然而,这些代谢物在SDM组和NADKD组之间差异无统计学意义,为研究NADKD的发病机制和筛选NADKD的生物标志物提供了见解。Xu等[26]采用基于UPLC-MS的综合代谢组学及模式识别技术,鉴定出与DKD相关的19种差异表达内源代谢物,为进一步探索DKD提供了方向。Ma等[27]采用基于UPLC-MS的非靶向代谢组学分析DKD患者的尿液代谢物,鉴定出147种尿代谢产物,5种代谢途径与DKD病理生理相关,泛酸和辅酶A生物合成途径的改变在DKD患者中最为明显。研究表明,泛酸将作为与DKD发生和进展相关的一种新的预测性生物标志物。此外,研究结果为泛酸和辅酶A生物合成途径可能成为DKD治疗的潜在靶点提供了广阔的前景。Mogos等[28]采用UPLC谱联用电喷雾电离四极杆飞行时间质谱(UPLC coupled with quadrupole time-of-flight electrospray ionization mass spectrometry,UHPLC-QTOF-ESI* MS)对90例2型糖尿病患者的血液和尿液进行了综合代谢组学分析,结果表明在尿中O-磷苏氨酸、天冬氨酸、5-羟基赖氨酸、尿酸和甲氧基色氨酸是区分健康对照组和DKD组以及不同蛋白尿分组之间的相关代谢物,这些潜在的生物标志物的鉴定表明它们可能参与了早期DKD和2型糖尿病的进展,但是需要进一步的靶向代谢组学纵向研究来验证研究结果。Mogos等[28]使用UHPLC-QTOF-ESI* MS技术,表明血清中的甘氨酸和犬尿喹啉酸、尿液中的色氨酸和替格列甘氨酸可以被认为是早期DKD的潜在生物标志物,但需要更多的研究来验证这些结果。

代谢组学可以反映机体的生理或病理状态,但其结果可能随年龄、性别、饮食、疾病状态、环境变化或者治疗干预等因素的变化而变化,且由于样本量小、结果异质性大和缺乏综合验证研究,大多数DKD生物标志物仍未被识别,难以开展生物标志物验证和临床评价的系统性工作。尽管存在这些挑战,但在DKD研究中使用代谢组学的潜在益处是巨大的。

5　多组学

在实际研究中,一类组学研究只能与疾病进行相关性分析,主要反映疾病过程的变化,不能解释因果关系。多组学通常是指以基因组学、转录组学、单细胞组学、蛋白质组学和代谢组学等为代表的多种高通量筛选技术的交叉应用,对人类疾病的研究有很大的促进作用。整合不同类型的组学数据可以阐明疾病的潜在致病变化,然后在进一步的分子研究中进行验证。通过整合多组学,可以过滤出生物分子与疾病表型之间的新关联,识别相关的信号通路,并建立详细的疾病生物标志物,同时了解DKD潜在的治疗靶点。多组学有望为理解DKD机制和发现潜在的生物标志物提供前所未有的视角。Jiang等[29]整合了代谢组学和肽组学来研究DKD发病过程中的生物学变化,发现10种代谢物和6种多肽在DKD不同阶段被逐步调控,显著提高了早期DKD诊断和DKD状态判别的准确性。Yang等[30]以人肾小球内皮细胞为细胞模型,采用代谢组学UPLC-MS和基于蛋白质组学串联质量标签的LC-MS法,推测DKD患者提取的血清外泌体可能主要通过上调凝血因子纤维蛋白原α亚基和下调1-甲基组氨酸引起内皮功能障碍。Liu等[31]采集血清进行蛋白质组学和大规模代谢组学整合分析,提高了区分DKD状态的诊断和预测的稳定性和准确性,为DKD的早期预警和诊断提供了稳定、准确的生物标志物。Zhao等[32]对50例经活检证实的DKD患者和25例对照组的肾小球样本进行转录组学和蛋白质组学整合分析,首次揭示了选择性多聚腺苷化的3′-UTR延长通过提高相应蛋白的翻译参与DKD的进展,为研究DKD的机制提供了新的见解。Wei等[33]应用LC-MS和下一代测序,以及串联质谱标签标记技术来评估DKD小鼠和模型小鼠之间的mRNA、蛋白质和修饰磷酸化位点,研究发现,RAS、RAP1、AMPK、PPAR和HIF-1等信号通路对DKD的发病机制至关重要。通过这种方法,发现靶向特定分子、蛋白质、激酶和关键通路可能是治疗DKD的一种有前途的方法。Sharma等[34]使用多组学方法将代谢物腺嘌呤鉴定为早期DKD进展的无创生物标志物,利用空间代谢组学、单细胞转录组学和实验研究,结果表明雷帕霉素靶蛋白(mechanistic target of rapamycin,mTOR)通路与腺嘌呤介导的组织纤维化有关,证明多组学有揭示DKD机制和靶向治疗的潜力。

整合多组学可以从多系统、多层次、多水平、多角度解释疾病的发展过程,描述疾病特征,对全面认识疾病至关重要,有着很大潜力;但也面临很大挑战,多组学之间相互调控的机制及数据集成较为复杂,且检测技术价格昂贵,临床大规模应用仍然受限。

6　小结与展望

DKD增加糖尿病患者的死亡率,已成为一个巨大的全球健康挑战。DKD发病机制复杂,并相互调控,不能简单地将其拆分后进行独立研究,而更应运用“系统生物学”思想多层面、多角度进行探索。DKD的典型进展被描述为蛋白尿和肾小球滤过率降低,然而上述临床指标在用于DKD诊断时存在一定的局限性,临床迫切需要更灵敏、更准确的生物标志物来进行DKD的早期诊断和进展评估。理想生物标志物应具备高度灵敏、特异、无创、易获取、性质稳定等特征。

组学和高通量筛选等新技术为DKD理想标志物的筛选提供更多的思路。单组学技术在疾病研究中并不能充分发挥其应用价值,各种组学数据的整合将有助于阐明疾病的潜在

致病变化，并可以在进一步的分子研究中进行验证。随着多组学技术的不断发展，可以过滤出生物分子与疾病表型之间的新关联，识别相关的信号通路，并建立详细的疾病生物标志物，对DKD早期诊断、疗效监测及预后评估有重要意义，同时也为发病机制的研究和治疗靶点的探寻提供新的线索，更有助于靶向个体化精准医疗的实现。

利益冲突　无

参考文献

[1] Yu MG, Gordin D, Fu JL, et al. Protective factors and the pathogenesis of complications in diabetes[J]. Endocr Rev, 2024, 45(2): 227-252.

[2] Wang N, Zhang C. Recent advances in the management of diabetic kidney disease: slowing progression[J]. Int J Mol Sci, 2024, 25(6): 3086.

[3] Büttner F, Barbosa CV, Lang H, et al. Treatment of diabetic kidney disease. A network meta-analysis[J]. PLoS One, 2023, 18(11): e0293183.

[4] 陈玉强，汪年松. 糖尿病肾病的诊治现状[J]. 中国临床医生杂志，2020，48(5)：508-511.

[5] Wu L, Zhao YY, Li MR, et al. Clinical and pathological characteristics of DKD patients with early-onset type 2 diabetes[J]. J Diabetes Complications, 2023, 37(8): 108520.

[6] 中华医学会糖尿病学分会微血管并发症学组. 中国糖尿病肾脏病防治指南(2021年版)[J]. 中华糖尿病杂志，2021，13(8)：762-784.

[7] 程璐，付平. 糖尿病肾病的诊断与鉴别诊断——肾活检在糖尿病肾病诊断中的应用[J]. 中国实用内科杂志，2017，37(3)：192-194.

[8] Vandereyken K, Sifrim A, Thienpont B, et al. Methods and applications for single-cell and spatial multi-omics[J]. Nat Rev Genet, 2023, 24(8): 494-515.

[9] Prokop JW, May T, Strong K, et al. Genome sequencing in the clinic: the past, present, and future of genomic medicine[J]. Physiol Genomics, 2018, 50(8): 563-579.

[10] Maeda S. Genome-wide search for susceptibility gene to diabetic nephropathy by gene-based SNP[J]. Diabetes Res Clin Pract, 2004, 66(Suppl 1): S45-S47.

[11] 任晓梅，杨景锋，刘启玲，等. 基于基因组学探讨糖尿病肾病的发病原因及其与心血管疾病的关系[J]. 西安交通大学学报(医学版)，2018，39(2)：266-270.

[12] Costa V, Angelini C, De Feis I, et al. Uncovering the complexity of transcriptomes with RNA-seq[J]. J Biomed Biotechnol, 2010, 2010: 853916.

[13] Hodgin JB, Nair V, Zhang HY, et al. Identification of cross-species shared transcriptional networks of diabetic nephropathy in human and mouse glomeruli[J]. Diabetes, 2013, 62(1): 299-308.

[14] Wu JS, Wang ZH, Cai MC, et al. GPR56 promotes diabetic kidney disease through ENOS regulation in glomerular endothelial cells[J]. Diabetes, 2023, 72(11): 1652-1663.

[15] Chen L, Su W, Chen H, et al. Proteomics for biomarker identification and clinical application in kidney disease[J]. Adv Clin Chem, 2018, 85: 91-113.

[16] Pino L, Banarjee R, Basisty N. A bright future for proteomics of health and disease. Introduction to the US HUPO 2021 themed issue-proteomics from single cell to systems biology in health and disease[J]. Mol Omics, 2022, 18(10): 894-895.

[17] 邓林，王少清，李萃萃，等. 蛋白质组学在糖尿病肾病诊断及治疗中的应用研究进展[J]. 保健医学研究与实践，2022，19(9)：171-176.

[18] Darmayanti S, Lesmana R, Meiliana A, et al. V-ATPase subunit C_1 and IKBIP as tandem prospective biomarkers for diabetic nephropathy[J]. Diabetes Res Clin Pract, 2023, 203: 110887.

[19] Li Q, Zhang J, Fang Y, et al. Phosphoproteome profiling of uEVs Reveals p-AQP2 and p-GSK3β as potential markers for diabetic nephropathy[J]. Molecules, 2023, 28(14): 5605.

[20] Fan XE, Xu MH, Chen X, et al. Proteomic profiling and correlations with clinical features reveal biomarkers indicative of diabetic retinopathy with diabetic kidney disease[J]. Front Endocrinol, 2022, 13: 1001391.

[21] Peng R, Zuo SY, Li X, et al. Investigating HMGB1 as a potential serum biomarker for early diabetic nephropathy monitoring by quantitative proteomics[J]. iScience, 2024, 27(2): 108834.

[22] 张倩，宋玮，梁晓春. 代谢组学在糖尿病神经病变研究中的应用和进展[J]. 中国医学科学院学报，2022，44(2)：313-317.

[23] 钟京谕，丁德芳，星月，等. 急性胰腺炎的影像组学和代谢组学研究进展[J]. 诊断学理论与实践，2024，23(4)：445-451.

[24] Luo YY, Zhang W, Qin GJ. Metabolomics in diabetic nephropathy: Unveiling novel biomarkers for diagnosis (Review)[J]. Mol Med Rep, 2024, 30(3): 156.

[25] Feng Q, Li YM, Yang YW, et al. Urine metabolomics analysis in patients with normoalbuminuric diabetic kidney disease[J]. Front Physiol, 2020, 11: 578799.

[26] Xu JN, Yuan Q, Wu K, et al. Effects of Bailing capsule on diabetic nephropathy based on UPLC-MS urine metabolomics[J]. RSC Adv, 2019, 9(62): 35969-35975.

[27] Ma T, Liu TH, Xie PF, et al. UPLC-MS-based urine nontargeted metabolic profiling identifies dysregulation of pantothenate and CoA biosynthesis pathway in diabetic kidney disease[J]. Life Sci, 2020, 258: 118160.

[28] Mogos M, Socaciu C, Socaciu AI, et al. Metabolomic investigation of blood and urinary amino acids and derivatives in patients with type 2 diabetes mellitus and early diabetic kidney disease[J]. Biomedicines, 2023, 11(6): 1527.

[29] Jiang XR, Liu XY, Qu XT, et al. Integration of metabolomics and peptidomics reveals distinct molecular landscape of human diabetic kidney disease[J]. Theranostics, 2023, 13(10): 3188-3203.

[30] Yang J, Liu DW, Liu ZS. Integration of metabolomics and proteomics in exploring the endothelial dysfunction mechanism induced by serum exosomes from diabetic retinopathy and diabetic nephropathy patients[J]. Front Endocrinol, 2022, 13: 830466.

[31] Liu SJ, Gui Y, Wang MS, et al. Serum integrative omics reveals the landscape of human diabetic kidney disease[J]. Mol Metab, 2021, 54: 101367.

[32] Zhao TT, Zhan DD, Qu S, et al. Transcriptomics-proteomics Integration reveals alternative polyadenylation driving inflammation-related protein translation in patients with diabetic nephropathy[J]. J Transl Med, 2023, 21(1): 86.

[33] Wei L, Gao JJ, Wang LZ, et al. Multi-omics analysis reveals the potential pathogenesis and therapeutic targets of diabetic kidney disease[J]. Hum Mol Genet, 2024, 33(2): 122-137.

[34] Sharma K, Zhang G, Hansen J, et al. Endogenous adenine mediates kidney injury in diabetic models and predicts diabetic kidney disease in patients[J]. J Clin Invest, 2023, 133(20): e170341.

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