脂质组学在糖尿病肾病研究中的应用进展*

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摘　要：糖尿病肾病（Diabetic nephropathy，DN）是导致糖尿病（Diabetes mellitus，DM）患者高死亡率的一种慢性并发症。诸多研究者致力于DN的诊断、病因、进展及治疗的分子机制。随着小分子脂质在肾功能和DN发病机制中调控作用逐渐清晰，脂质组学也成为DN研究中的有力工具。DN具有脂质代谢紊乱的特点，脂质组学因其特有的针对性，在DN的脂质代谢谱表征、诊断、机制探究及治疗方面发挥着重要的作用。但同时，机体内的脂质又是复杂的，这给脂质的检测与分析带来了巨大的挑战。未来多学科交叉及多组学的联用是脂质组学突破的方向。本篇文章概述了脂质组学在DN研究策略、脂质代谢谱表征、早期诊断、药物疗效及机制探索及组学联合分析中的应用进展，并进一步讨论了未来DN脂质组学应用的机遇与挑战，以期为相关方向的研究人员提供一个清晰的研究现状及前景。

关键词：糖尿病肾病　糖尿病　脂质组学　生物标志物　应用进展

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糖尿病肾病（Diabetic nephropathy，DN）是全球慢性肾病（Chronic kidney disease，CKD）和终末期肾病的主要病因[1]，也是导致糖尿病（Diabetes mellitus，DM）患者高死亡率的并发症。据报道，全球30%-50%的糖尿病患者会发展为CKD[2-3]，但因反映肾功能不全的多种干扰因素存在，特别是在2型糖尿病患者（Type 2 diabetes mellitus，T2DM）中，严重影响DN的流行病学研究和临床的精准诊断。随着全球糖尿病患病率的不断攀升，DN已成为危害人类健康的重大疾病，因此，对DN进行早期预防、诊断、探寻精准有效的治疗方法对降低DN患病率意义重大。

小分子脂质在人类健康和疾病中发挥多样而复杂的功能，在正常肾功能的调节和DN的发病机制中起重要作用[4-6]。在此背景下，国内外大量学者开始对DN的病因、发病进程及治疗过程的分子机制进行深入研究。相关证据表明，DN导致脂质代谢紊乱[7-9]，且脂质紊乱会加重慢性肾病及其他并发症的进展[10-12]。在1型糖尿病（Type 1 diabetes mellitus，T1DM）中，血清脂质谱被证明可以预测DN的发展和进展[13-14]。在T2DM中，酯化和非酯化脂肪酸、磷脂等脂质代谢物成为DN进展的生物标志物[15]，且脂质的含量与T1DM或T2DM患者肾小球滤过率（Estimated glomerular filtration rate，eGFR）的下降有潜在联系[16]。

作为代谢组学的一个分支，脂质组学这一新兴学科发展迅速，关键脂质介质分析已成为DN早期特异性生物标志物、临床用药疗效评价、改善疾病预后和药物机制探讨等方面的重要工具[17]。本文就脂质组学在DN研究中的应用进展，从DN脂质代谢谱表征、诊断、治疗及机制等方面进行综述总结。

1　脂质组学及其研究策略

脂质组学是利用分析化学的原理和技术对生物体内脂质进行研究的一门学科[18]。脂质组学能够通过单个脂质的变化来探究体内相关代谢过程，可以充分

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地了解在病理生理过程中的作用，为研究疾病状态下的脂质代谢变化提供强大的技术支持[19]。此外，脂质组学还可以揭示正常、病理或治疗特定事件的独特代谢特征，阐明所讨论物种的指纹和种群中性状的分布，同样也提供了监测生物体相关指标的基线，从而有助于推进生物体在疾病状态下的诊断、治疗及预后[20]。

在过去的20年中，脂质组学作为系统生物学中的一个新领域，在疾病诊断和生物标志物发现、药物开发、食品和营养研究等方面的应用广泛[21-22]。在脂质组学分析之前，需要进行适当的采样和样品储存。不同于质谱（Mass spectrum，MS）成像使用组织切片[23]，脂质组学技术多使用生物提取物[24-25]。定量脂质组学分析中，在脂质提取过程中添加适当的内标至关重要[26]，内标通常通过归一化添加到总蛋白、湿/干组织重量或液体体积中以进行脂质定量。提取脂质后，使用MS、核磁共振、气相色谱法、液相色谱法（Liquid chromatography，LC）、超临界流体色谱法、毛细管电泳法等分离分析技术进行脂质分析[27]。随后，结合多种生物信息学手段，机器学习、模型建立的不同算法对复杂的脂质组学数据进行数据分析处理（图1）。

当前，多种脂质组学的定量方法被开发。Manni等[28]针对神经酰胺和鞘磷脂类代谢物，对不同哺乳动物组织以及哺乳动物来源的细胞培养物进行了脂质组学的定量分析，两类物质在正电离模式的MS分析下拥有良好的一致性。对于较少见的脂质类别中的类固醇激素的定量分析，Drotleff等[29]证明了Q-TOF可以通过数据独立采集和所有理论碎片离子质谱的顺序窗口采集来实现雌二醇和睾酮的定量分析，并将此方法应用于一项临床测量男性志愿者的血浆性激素水平的量化研究中。随着相对定量与绝对定量的脂质组学方法的不断开发，进一步提高了生物标志物筛选和鉴定的效率及准确性。

2 脂质组学在DN脂质代谢谱表征中的应用现状

脂质组学已成为系统生物学中发现疾病生物标志物的工具[30-31]，脂质代谢紊乱或异常脂质将导致各种肾脏疾病[32-35]。因此，探究动物及人体的脂质代谢谱，对其应用的全面、深入地理解对脂质组学至关重要。

根据LIPID MAPS联盟（http://www.lipidmaps.org）提出的综合分类系统，脂质可分为8种不同的大类别[36]：脂肪酰（Fatty acyl，FA）、甘油酯（Glycerolipids，GL）、甘油磷脂（Glycerophospholipids，GP）、固醇脂（Sterol lipids，ST）、鞘醇酯（Sphingolipids，SP）、异戊烯醇脂（Prenol lipids，PR）、糖脂（Saccharolipids，SL）、聚酮类（Polyketides，PK）。8种类别脂质的结构及上下游关系如图2所示。随着高通量质谱技术的不断发展，越来越多的学者开始借助脂质组学，不断开发新的技术方法，以期对机体脂质做更广范围的检测与定量分析。在DN方面，van Meulebroek等[37]通过高分辨率全扫描Q-Exactive Orbitrap质谱法，比较了26名健康对照和17例T2DM患者的粪便中脂类代谢物的差异，实现了对粪便中127种脂类物质的检测，共涵盖了8种脂质类别，验证了非靶向技术建立脂质代谢图谱的方法适用性。Hou等[38]使用高通量靶向脂质组学方法，建立了正常大鼠肾皮层的脂质谱，包含437种脂质，涉及25种脂质类别，且进一步发现甘油脂质、溶血磷脂和鞘脂在DN大鼠的肾皮质显著增加，为鉴定临床DN中病理相关的脂质物种提供了可靠的数据支撑。近年来，外泌体在DN发生发展中的作用越来越引起人们的关注[39-40]。外泌体在维持细胞稳态和细胞间的信息交流起重要作用[41-44]，外泌体中包含脂质在内的多种成分，为分析外泌体中脂质[45]，创建了基于同位素标记和串联质谱的靶向脂质分析研究方法[46]，在HK-2细胞的外泌体中定量了218种脂质，差异脂质进

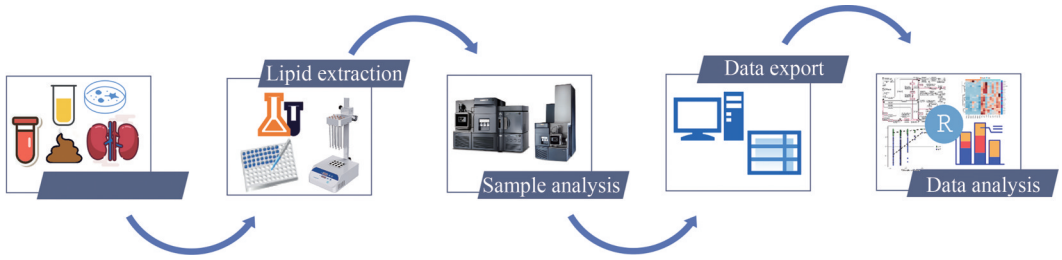

图1 脂质组学研究的实验流程

注：脂质组学研究可大致分为：样本收集、脂质提取、样本分析、数据导出和数据分析5个步骤。

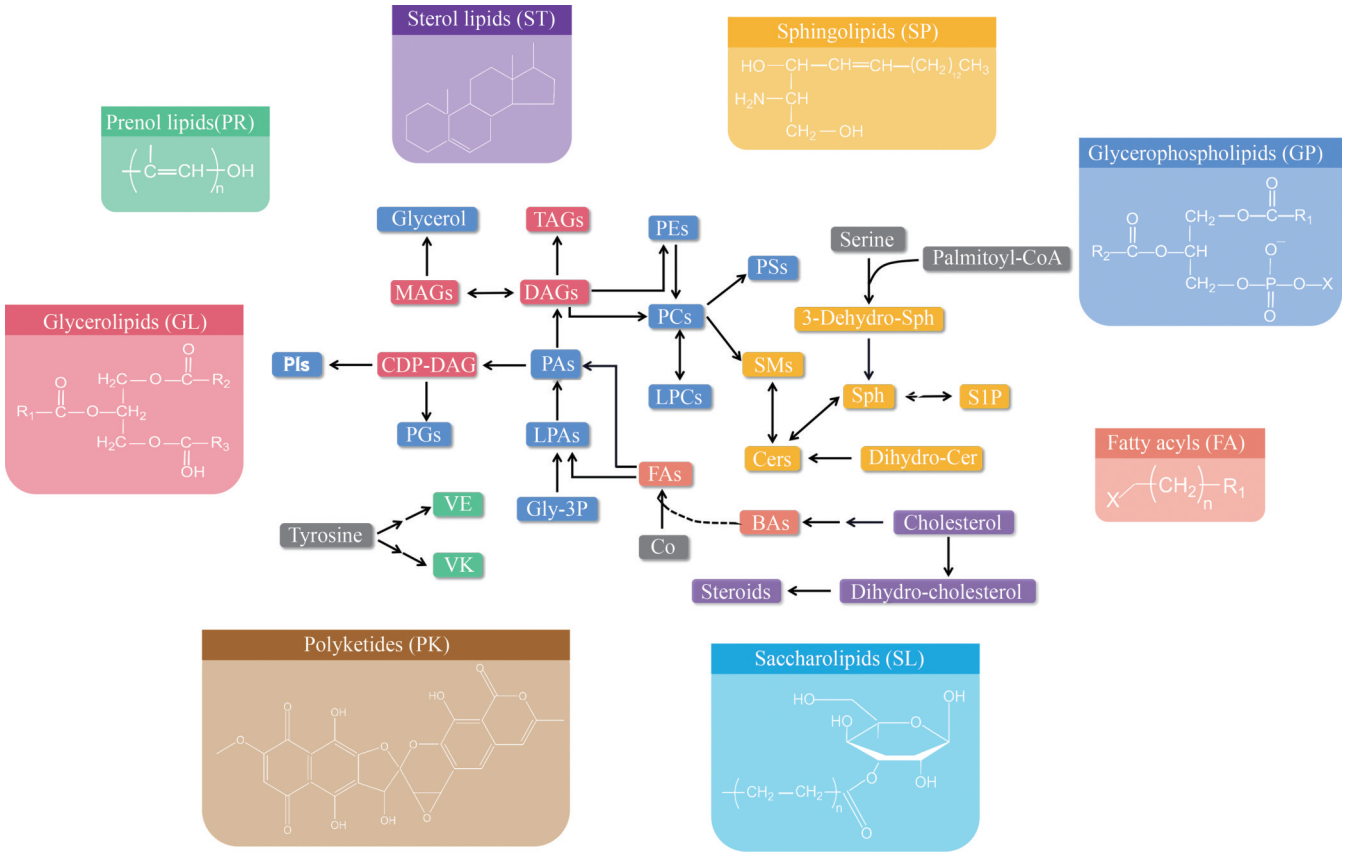

图2　脂质的分类和代谢途径

注：脂质可分为八种大类别：脂肪酰(Fatty acyl，FA)，甘油酯(Glycerolipids，GL)，甘油磷脂(Glycerophospholipids，GP)，固醇脂(Sterol lipids，ST)，鞘醇酯(Sphingolipids，SP)异戊烯醇脂(Prenol lipids，PR)，糖脂(Saccharolipids，SL)，聚酮类(Polyketides，PK)。

一步分析有助于为探索DN的机制提供新的靶点。仅有的研究提示，今后开展外泌体与DN相关的脂质组学研究工作将对DN的诊断和治疗提供更多的思路与方法。

3　脂质组学在DN早期诊断中的应用现状

DN的准确诊断仍是亟待解决的难点。最初，DN临床诊断通过检测白蛋白尿实现，然而部分患者有进行性DN但却无明显的蛋白尿，可变性在不断加重[47-49]。“金标准”组织病理学诊断因会对患者造成有创性伤害，在临床环境中应用受限[50]，而对于蛋白尿正常，eGFR下降为主要表现的DN患者，机体的肾小球基底膜增厚、系膜基质弥漫性增多乃至肾小球结节性硬化等肾脏病理在eGFR下降之前也早已出现[51]。因此，发掘DN的早期诊断的潜在生物标志物将有助于DN的预防和诊断，也是众多研究者努力的方向。Xu等[52]通过分析包括健康对照组、T2DM患者和DN患者在内的577名受试者血样，以探索血清中的脂质变化，最终发现LPE(16∶0)和TAG(54∶2)-FA(18∶1)的组合是预测DN的生物标志物组，同PE(16∶0/20∶2)在内的3个脂类标志物与DN的病理阶段密切相关。磷脂是生物膜的主要结构成分，诸多研究表明磷脂及其代谢与T2DM和DN的进展、加重密切相关[53-60]，通过收集112例临床受试者的血浆样品，表征了T2DM和DN的血浆磷脂，靶向定量了PI(C18∶0/22∶6)和SM(dC18∶0/20∶2)两种新型生物标志物，可作为预测T2DM和DN进展的指标[61]。磷脂中的溶血磷脂酸(Lysophosphatidic acid，LPA)和溶血磷脂酰胆碱(Lysophosphatidyl choline，LPC)被证实可在肾脏中积聚，可诱导肾脏炎症和糖尿病啮齿动物模型中的肾小管间质纤维化[62-63]。一项关于评估LPA和LPC是否与糖尿病肾病的发展有关的研究也同样表明，人体尿液中的总LPC和LPA与尿白蛋白水平极显著相关，且包括LPA(16∶0)、LPC(16∶0)在内的6种物质在疾病组显著高于对照组，推测与白蛋白共同排泄以及肾脏局部产生有关[64]。关于T1DM与DN之间的进展联系的脂质组

学研究也早已开展。研究者对来自高加索的669例T1DM患者的血清脂质组学检测，发现LPC、鞘磷脂与eGFR、白蛋白尿之间存在横断面关联，关键生物标志物SM(d18∶1/24∶0)与较低的白蛋白尿组进展风险相关[65]。类似的，通过调查了326名T1DM患者的血清脂质，并对部分脂质种类进行了量化，最终发现鞘氨醇是尿白蛋白的一个重要调节因素[66]。总之，越来越多的证据支持脂质和脂质代谢产物在肾脏疾病的诊断中发挥着重要作用。

4 脂质组学在DN药物疗效及机制探索的应用现状

脂质组学具有评价药物治疗效果的潜质[51,67]。在最近的研究中，对来自糖尿病db/db和db/db eNOS小鼠的肾皮层组织以及非糖尿病对照组进行了非靶向脂质组分析[68]，发现与db/db小鼠相比，db/db eNOS小鼠的肾脏疾病恶化严重破坏了机体脂质代谢平衡，特别是涉及甘油脂质的网络。当用肾素-血管紧张素系统(Renin-angiotensinsystem，RAS)抑制剂赖诺普利和氯沙坦治疗后，小鼠的DN表型及部分脂类特征被逆转，首次发掘了RAS抑制对肾脏甘油脂质代谢网络的作用。在机制探索方面，许多研究已表明，糖尿病实验动物和人类的肾脏中存在脂质积累，并且脂质影响DN的发病机制[69-70]，肾脏中的脂质堆积诱发肾脏的进胰岛素抵抗、氧化应激和内质网应激，最终导致肾脏结构和功能的恶化[71-74]，可能的机制包括累积的脂质增加了血管内皮生长因子和转化生长因子-β的表达，促进蛋白尿和糖尿病肾小球硬化[75]。

5 脂质组学与其他组学联合在DN研究中的应用现状

DN病因与发病机制具有复杂性，对DN进行多组学联合分析，可以更好地表征这种病理生理学背后的分子关系。当前，包括基因组学、转录组学、蛋白质组学、代谢组学和脂质组学在内的系统生物学可以对细胞代谢和生物网络进行实时分析[76-78]。多组学的联合分析使基因-蛋白-代谢物-细胞-器官调节机制在多水平上的连接成为可能，为预防、诊断、预后和治疗开发更可靠和特异性的生物标志物提供了更可靠的依据[79-80]。对于DN来说，整合肾脏功能的分子和细胞生物学，可以全面地为DN机制研究提供新的思路与见解。

神经酰胺是参与各种细胞过程的生物活性脂质，通过调控细胞凋亡、TGF-β信号传导和炎症参与肾损伤[81-86]。基于此，Sas等[87]利用高度灵敏和特异性MS方法定量测量来自DN和对照组的C57BLKSdb/db小鼠模型的血浆和肾脏皮层中的脂质，发现肾脏和血浆神经酰胺水平与DN的功能和组织病理学特征相关，结合转录组学分析显示，小鼠肾组织神经酰胺合成减少，向鞘氨醇和下游鞘氨醇-1-磷酸信号传导增加，系统地揭示了神经酰胺代谢在DN中的作用。一项脂质组学和转录组学综合分析的临床研究，随访了92名患有T2DM的美国印第安人，确定了血清中DN进展的脂质组学预测因子，构建的差异网络反映了在DN进展状态中各种脂质之间的相互作用[88]。通过整合脂质组学、转录组学和网络药理学分析，阐明了当归补血汤的活性成分通过下调Degs2和Cers基因的表达来改善DN，并通过作用于诸多靶点来减少脂质的积累，这些作用发生在AGE-RAGE、鞘脂和各种炎症相关的信号通路中，且认为神经酰胺是糖尿病神经病变的重要生物标志物[89]。Perkins等[90]以由1430名参与者(535例和895名对照组)构成的T1DM队列为研究对象，采用靶向代谢组学、脂质组学和蛋白质组学联合技术平台，发现和验证一组与T1DM中eGFR快速下降相关的生物标志物，并开发了一种量化游离脂肪酸、酰基肉碱和其他的复杂脂质类的靶向测定法。此外，最近一项关于DN进展的研究[91]，基于发现和验证队列研究，运用深度学习筛选关键脂质和蛋白特征，通过多组学关联网络揭示了Cer(d18∶1/16∶0)在疾病进展过程中的关键作用，为寻找DN相关的生物标志物及治疗新靶点提供了新的研究思路。尿液因易于收集、简便地分析前处理，以及蛋白质较高稳定性等因素，成为组学生物标志物评价的重要来源[92-94]。Magagnotti等[95]对诊断为T1DM的儿童的尿液进行了蛋白质组学分析，同时应用了尿液脂质组学方法，首次发现了前列腺素和神经酰胺的脂质代谢与DN病变相关。总之，脂质组学与其他组学联合应用的系统生物学方法，为研究DN开辟了崭新广阔的前景，并提高了对DN背后的分子相互作用及功能特性的认识。

6 分析与展望

关于DN的脂质组学研究现阶段已经朝着两个方向发展：靶向分析或非靶向分析，两者结合对于研究DN信号处理、脂质代谢、生物标志物和分子机制的挖

掘非常有利，为高效、快速、准确地筛选潜在生物标志物提供了有力手段。然而，绝对意义的靶向脂质组学依然有很大进步空间，且目前脂质小分子的变化仅一定程度上反映了有关疾病进展状态，关于脂质组学在DN方面的应用潜在价值尚未被充分挖掘，重复的方法思路将阻碍我们释放脂质组学的真正力量。

基于此，未来DN的相关脂质组学可以从以下4个方面深入研究：①优化脂质组学分析技术，比如通过衍生化增加脂质类别和分子物种的覆盖率、研究合成更多的脂质分子标准品、开发更高提取效率的方法，将对开发基于LC的脂质组学方法更为适用。②脂质组学仅是疾病研究中的一个方面，将脂质组学与其他组学策略（如基因组、转录组、蛋白质组、代谢组学）整合，可以最大限度地弥补脂质组学的不足，通过不同分子层面的数据集分析对DN开展系统性研究，在不同分子物种水平进行代谢途径重建和通量分析，绘制全面的脂质数据的途径图谱将有助于DN潜在机制的深入了解，促进脂质生物标志物在临床诊断方面的研究。③脂质类别和物种具有结构多样性的特点，通过稳定同位素标记的代谢流分析技术，可以揭示DN脂质代谢中的通路活性，综合代谢物浓度和流量以更好地表征机体脂质代谢的变化。④当前外泌体及单细胞脂质组学的热度在逐步升高，开展有关DN外泌体和/或单细胞脂质组学的研究，拓展了脂质在生物医学科学中的视角，进而有助于DN复杂病理生理机制的揭示。

7 小结

当前，有效的诊断、鉴别糖尿病和DN患者，并及时实施肾保护的管理策略是预防和治疗DN的有效措施。脂质已被确定为DN发病机制的潜在因素，其在探索DN的诊断、预防、治疗等方面发挥着不可忽视的重要作用。未来，高通量检测方法的开发、多组学的联用、外泌体及单细胞脂质组学等新技术的应用，将更大限度地推动脂质组学对DN的贡献，推动DN精准靶向干预与治疗，最终改善人类健康。

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Application Progress of Lipidomics in Diabetic Nephropathy

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Abstract: Diabetic nephropathy (DN) is a chronic complication that leads to the high mortality of diabetes mellitus (DM) patients. Many researchers are devoted to the diagnosis, etiology, process and molecular mechanism of treatment of DN. At present, the regulation of small molecular lipids on renal function and the role in the pathogenesis of DN are gradually becoming clear, and lipidomics has also become a powerful tool in DN research. DN is characterised by disorders of lipid metabolism, and lipidomics plays an important role in the characterisation of lipid metabolic profiles, diagnosis, mechanistic investigation and treatment of DN because of its unique relevance. But at the same time, the lipids in the body are complex, which brings great challenges to the detection and analysis of lipids. In the future, multidisciplinary crossover and multi-omics association is the direction of lipidomics breakthrough. This article outlines the progress of the application of lipidomics in DN research strategies, lipid metabolic profiling, early diagnosis, drug efficacy and mechanism exploration, and histological co-analysis, and further discusses the opportunities and challenges of the future application of lipidomics in DN, with the aim of providing a clear picture of the current status of the research and the prospects for researchers in the relevant directions.

Keywords: Diabetic nephropathy, Diabetes mellitus, Lipidomics, Biomarkers, Application progresss

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