空间代谢组学在中枢神经系统疾病研究中的应用进展

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摘要: 中枢神经系统 (central nervous system, CNS) 是人体功能调控核心, 脑区结构与代谢网络具有显著异质性, 不同脑区代谢特征精准分工。阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)、缺血性脑卒中 (ischemic stroke, IS) 等CNS疾病, 病理机制常伴随特定脑区代谢紊乱, 且该紊乱早于宏观结构损伤, 可从中寻找疾病早期诊断标志物。然而传统诊断及疗效评估方法在辨识早期代谢水平细微异常、表征代谢物空间分布特征、精确判定治疗是否逆转病理关联代谢紊乱方面存有限制。空间代谢组学基于质谱成像技术, 能在微米级空间分辨率下, 实现CNS组织切片中数百种代谢物的原位检测与空间定位, 既填补疾病早期代谢异常检测技术空白, 又推动疾病病理机制研究从“宏观结构”向“分子空间网络”跨越, 为疾病生物标志物筛选、机制解析与药物疗效评估提供重要技术支撑。本文系统综述空间代谢组学主要技术, 深入探讨其在CNS疾病研究中的应用现状, 旨在为推动该领域代谢组学发展提供理论支持与实践参考。

关键词: 中枢神经系统疾病; 空间代谢组学; 质谱成像; 阿尔茨海默病; 帕金森病; 缺血性脑卒中

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The application of spatial metabolomics in the research of central nervous system diseases

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Abstract: The central nervous system (CNS) serves as the core for regulating human body functions. The structural and metabolic networks of brain regions exhibit significant heterogeneity, with distinct brain regions having precisely divided metabolic characteristics. For CNS diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and ischemic stroke (IS), their pathological mechanisms are often accompanied by metabolic disorders in specific brain regions. Notably, such metabolic perturbations precede macroscopic structural damage, thus providing a promising avenue for the identification of biomarkers for the early diagnosis of these disorders. However, traditional diagnostic methods and therapeutic effect assessment approaches have limitations. Specifically, they fall short in identifying subtle abnormalities in early metabolic levels, characterizing the spatial distribution of metabolites, and accurately determining whether treatments can reverse the metabolism-related pathological disorders. Based on mass spectrometry imaging technology, spatial metabolomics enables *in situ* detection and spatial localization of hundreds of metabolites in CNS tissue sections at a spatial resolution of the micrometer level. It not only fills the gap in technologies for detecting early metabolic abnormalities in diseases but also drives the research on disease pathological mechanisms from the "macroscopic structure" to the "molecular spatial network" level. Consequently, it provides crucial technical support for the screening of disease biomarkers,

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the analysis of disease mechanisms, and the evaluation of drug therapeutic effects. This article systematically reviews the main technologies of spatial metabolomics and deeply explores its current application status in CNS disease research. The aim of this review is to offer theoretical support and practical references for advancing the development of metabolomics in this field.

Key words: central nervous system disease; spatial metabolomics; mass spectrometry imaging; Alzheimer's disease; Parkinson's disease; ischemic stroke

中枢神经系统 (central nervous system, CNS) 是人体稳态调控[1,2]与高级神经功能实现的核心枢纽, 其结构以脑和脊髓为两大功能主体[3], 通过复杂的神经环路与信号传导网络, 主导机体多种重要生命活动调节。CNS疾病指中枢结构或功能异常引发的神经障碍, 包括脑血管病、神经退行性疾病、脑肿瘤、中枢感染、脑外伤及癫痫等。CNS疾病具有症状复杂、治疗难度大、易遗留功能残疾、死亡率高等特点[4-9]。在CNS疾病研究中, 传统影像学如计算机断层扫描 (computed tomography, CT)、核磁共振成像 (magnetic resonance imaging, MRI) 等虽可呈现脑组织结构或功能异常, 却难以揭示分子层面代谢紊乱, 对早期微小病变识别灵敏度不足[10,11]; 病理组织学检查虽能提供细胞层面信息, 但无法动态监测疾病进展及时空异质性[12,13]。

空间代谢组学基于质谱成像, 是一种无需标记、能够直接从组织切片中对数百种代谢物和药物进行空间定位绘图的技术。该技术可在保留组织空间位置信息的前提下, 对CNS内多种代谢物进行高分辨率、高通量的同步检测, 精准捕捉病变区域的代谢特征变化, 评估CNS微环境中的病变异质性, 避免传统方法因缺乏空间定位导致的信息模糊, 为病理机制与新药研发提供全面分子依据[14-17]。空间代谢组学为CNS疾病生物标志物发现、病理机制理解以及相关治疗药物在脑组织内的分布分析提供助力。

本文系统概述了空间代谢组学的基本原理与流程、主要技术手段, 重点介绍了空间代谢组学在CNS疾病领域的应用, 包括病理机制、生物标志物发现以及药物研究等, 以期为CNS疾病的深入研究提供技术支撑和参考。

1 空间代谢组学概述

1.1 基本原理与流程

空间代谢组学是融合代谢组学分析与空间定位技术的前沿方法, 可在保留组织、器官等生物样本空间结构信息的同时, 实现代谢物的定性定量及空间定位分析[14,18]。该技术通过解析代谢物的空间分布特征, 为疾病病理机制阐释、生物标志物筛选及创新药物研发提供关键科学依据。

基于质谱成像的空间代谢组学主要流程包括样品制备、质谱数据采集、数据处理与成像三大核心环节[19]。样品制备是决定成像质量的关键前提, 核心目标是在不破坏样品中成分空间分布的前提下提升成分离子化效率, 需根据样品类型选择多聚甲醛、福尔马林、丙酮、乙醇等固定或冷冻保存等方式防止成分降解与移位[20-22]。在样品固定过程中, 多聚甲醛和福尔马林固定会显著降低低分子量代谢物 (质荷比 < 500) 的离子信号, 而丙酮和乙醇固定则可增强低分子量代谢物的离子信号; 多聚甲醛和乙醇固定的组织中, 脂质的离子强度显著下降, 而福尔马林和丙酮固定对脂质检测几乎无影响[23]。质谱数据采集旨在建立“空间坐标–成分信号”关联, 通过质谱仪对样品表面逐点面扫描, 需设定空间分辨率及扫描范围, 利用基质辅助激光解吸电离 (matrix-assisted laser desorption ionization, MALDI)、解吸电喷雾电离 (desorption electrospray ionization, DESI) 等离子源对各扫描点成分离子化后, 由检测器捕捉离子信号得到质谱图, 系统自动将质谱数据与X/Y轴空间坐标绑定形成原始数据集[24,25]。数据处理与成像环节通过专业软件将原始数据转化为可视化图像, 先经去噪、质量轴校准、强度归一化等预处理筛选有效离子信号, 再将信号与代谢物、脂质等已知数据库比对识别具体成分, 最后以离子强度对应颜色深浅, 结合空间坐标生成2D或3D分布热图, 直观呈现成分在样品中的空间分布[14]。其分析流程如图1所示。

1.2 空间代谢组学技术方法

空间代谢组学的核心技术体系为质谱成像技术 (mass spectrometry imaging, MSI), 这是一种新型的分子成像技术, 它能够直接从样品表面原位收集分子信息, 具有高空间分辨率, 可以同时可视化各种化合物的空间分布和相对含量[26,27]。MSI技术的电离技术主要涵盖基质辅助激光解吸电离质谱成像 (matrix-assisted laser desorption ionization mass spectrometry imaging, MALDI-MSI)、解吸电喷雾电离质谱成像 (desorption electrospray ionization mass spectrometry imaging, DESI-MSI)、二次离子质谱成像 (secondary ion mass spectrometry imaging, SIMS imaging)、与空气动力辅助

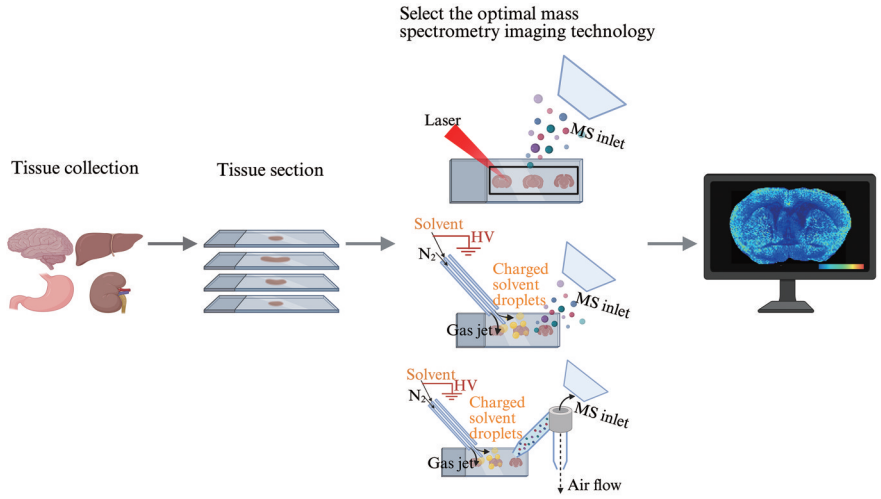


Figure 1 The flow chart for spatial metabolomics. MS: Mass spectrometry; HV: High voltage

解吸电喷雾电离质谱成像 (air flow-assisted desorption electrospray ionization mass spectrometry imaging, AFADESI-MSI) 等。其中, MALDI-MSI、DESI-MSI 与 AFADESI-MSI 因兼具空间分辨率、检测灵敏度及组织兼容性等技术优势, 为 CNS 疾病的病理机制研究及生物标志物发现提供了重要的技术支撑。

1.2.1 MALDI-MSI MALDI-MSI 的工作原理如图 2A, 样品与过量小分子基质共结晶, 激光照射时基质吸能瞬间气化, 能量传递给样品分子, 使其从基质晶格解吸并离子化, 基质与样品形成的弱相互作用复合物气化时产生气相离子, 随后进入质谱仪分析[28]。作为目前使用最广泛的软电离质谱成像技术[29], MALDI-MSI 能够在相对温和的条件下使大分子物质离子化, 减少了大分子物质在电离过程中的碎片产生[30]。与其他电离技术相比, 它能够更好地保持大分子物质的完整性, 在分析大分子物质时具有显著的优势[31]。Casas-Rodríguez 等[32]基于 2,5-二羟基苯甲酸基质的 MALDI-MSI 技术, 分析了大鼠肠道组织中柱孢藻毒素 (cylindrospermopsin, CYN) 脂质谱的改变, 为阐释 CYN 诱导的炎症反应、氧化应激及细胞膜损伤机制提供了空间分布证据。Liu 等[33]研究发现基于咖啡酸基质, MALDI-MSI 技术对动/植物组织样本蛋白质的原位检测质量上限接近 200 000 Da。因此, 借助 MALDI 为电离方式的 MSI 技术多应用于脂质[34]、蛋白质[35]以及多肽[36,37]。

基质沉积是影响 MALDI-MSI 检测效能的核心环节[38], 其选择直接关乎可检测分子类型、电离效率及结果重现性。该技术早期主要用于大分子成像分析, 这一局限性主要归因于低质荷比区间存在显著的基质源性化学噪声[39,40], 此类背景信号会抑制小分子离子的有效检测。随着基质筛选技术、样品制备方案的发展, 当前已实现小分子物质的精准成像[41,42]。MALDI-MSI

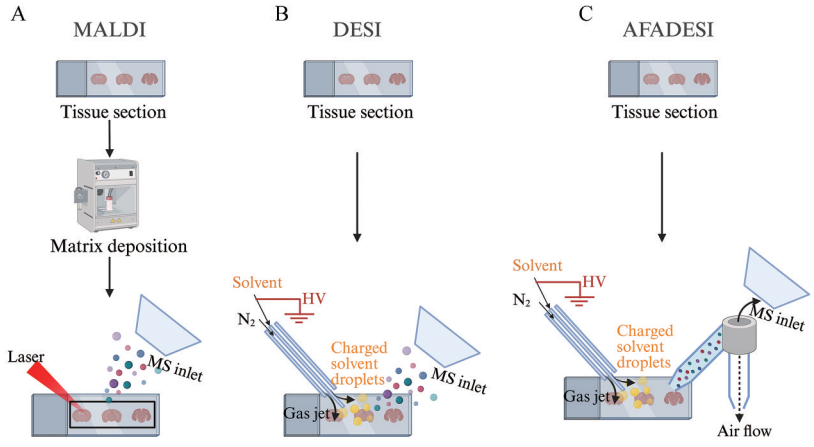


Figure 2 The flow chart of ionization principles. A: MALDI ion source; B: DESI ion source; C: AFADESI ion source. MALDI: Matrix-assisted laser desorption ionization; DESI: Desorption electrospray ionization; AFADESI: Air flow-assisted desorption electrospray ionization

具有较高的空间分辨率, 但是实现高的空间分辨率需缩小激光光斑直径, 离子产率通常会随之下降[43,44]。因此开展空间代谢组学研究时, 需要在高的空间分辨率与足够的信号强度之间进行权衡。此外, MALDI-MSI需在真空环境下运行, 样品预处理阶段通常需进行基质沉积处理增加了MALDI-MSI操作的复杂性。

1.2.2 DESI-MSI与AFADESI-MSI DESI与AFADESI均属于常压敞开式离子化技术, 无需样品预处理、非真空环境下实现样品表面化学成分的原位电离与空间分布分析。不同之处在于DESI源采用单一电喷雾源, 带电液滴直接撞击样品表面, 依赖液滴动能和解吸作用完成电离[45,46], 如图2B。AFADESI源在DESI源基础上优化, 引入辅助气路系统 (如干燥氮气), 通过气流约束喷雾方向, 随后利用气流将离子长距离输送, 显著扩大了成像视野的长度与面积[47,48], 如图2C。与MALDI-MSI不同, DESI-MSI与AFADESI-MSI均是常压质谱成像技术, 因此两者操作更简便, 可通过对探针的设计实现小样本精细分析与大样本快速扫描成像[49], 为实时诊断提供了可能[50]。有研究报道DESI-MSI结合Lasso统计方法, 能精准区分胰腺正常组织与癌组织, 实现手术切缘的术中实时分子评估[51]。此外, DESI与AFADESI无需基质沉积[52,53]。因此, 它们不会像MALDI技术那样, 面临因样品移动而导致空间定位误差的高风险[47,54]。不仅如此, AFADESI-MSI在DESI-MSI的电喷雾离子源中引入高速气流 (如45 $L \cdot min^{-1}$空气流)[55], 通过气流与传输管协同作用增强带电液滴的远距离传输效率, 使离子化过程更高效、脱溶剂更彻底, 从而将检测灵敏度提升至pg级, 动态范围扩展至3个数量级, 如大鼠肾脏组织中的甜菜碱最高强度离子 (m/z 140.068 3, 强度1.2×10^6) 与最低强度离子 (m/z 142.074 9, 强度1.1×10^3) 的强度比值超过1.0×10^3。覆盖胆碱、脂质、核苷酸等10余类共1 500余种代谢物[56]。如AFADESI-MSI在应用于食管癌代谢机制研究时, 发现吡咯啉-5-羧酸还原酶2等新型代谢酶的异常表达, 而此类低丰度分子在传统DESI-MSI中难以被有效检测[57]。除此之外, 对小尺寸样本的精细结构微区进行可视化分析, AFADESI-MSI比DESI-MSI更具优势[58]。但是, DESI与AFADESI的空间分辨率均不及MALDI。在钩虾体内有机污染物及其生物转化产物空间分布研究中, DESI可检测全部6种母体化合物, 对小分子污染物更灵敏但存在部分背景干扰; MALDI虽仅检测到4种母体化合物, 却能识别肝胰腺等组织的特异性生物标志物, 空间分辨率更优[59]。通过探针结构、扫描策略和喷雾条件的优化, 也可在一定程度上提高DESI与AFADESI的空间分辨率, Yu等[60]通过设计20 μm内径离轴喷雾探针, 搭配逐点光栅烧蚀扫描策略, 优化喷雾溶剂为9∶1的乙腈–水溶液, 流速设为5 $\mu L \cdot min^{-1}$, 最终实现30 μm空间分辨率。

三种空间代谢组学常用MSI技术的进一步对比信息见表1[61-67]。此外, SIMS imaging虽作为空间分辨率极高的MSI技术[68], 但由于其检测范围较窄, 主要聚焦小分子代谢物[69], 离子化过程对样本存在溅射损伤, 且灵敏度受分析物分子结构影响较大, 更多应用于特定微区域的精细代谢特征解析, 而非大规模组织的全代谢组覆盖研究, 因此本文不将其划分为在空间代谢组学常用的MSI技术。

2 空间代谢组学在CNS疾病研究中的应用

空间代谢组学通过精准定位CNS内代谢物的空间分布、定量变化及相互作用, 在疾病机制探究、早期生物标志物筛选、药物作用靶点发现与疗效评估等方发挥关键作用, 已广泛应用于阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)、缺血性脑卒中 (ischemic stroke, IS)、抑郁症、脑肿瘤等研究中, 为CNS疾病的病理机制阐明、生物标志物的发现及药物研发提供重要支撑。

2.1 阿尔茨海默病

AD作为一种典型的神经退行性疾病, 以进行性记忆衰退和认知功能障碍为主要临床特征[70]。传统技术存在依赖抗体标记、丢失空间信息、空间分辨率低等局限, 难以揭示AD复杂病理网络的空间关联。近年来, 空间代谢组学技术的突破性发展为AD研究提供了全新的技术范式。该技术通过高分辨率解析脑区组织的代谢分子空间分布特征, 为揭示AD病理机制、筛选新型生物标志物及药物研究提供了强有力的技术支撑, 推动AD研究从传统病理分析向代谢调控机制研究的深度拓展。

β淀粉样蛋白 (β-amyloid protein, Aβ) 斑块形成是AD的主要病理特征, 并且是推动AD发病机制的潜在关键早期诱导因素[71]。Michno等[72]采用代谢同位素标记技术结合MALDI-MSI可以直观呈现不同脑区单个斑块内Aβ的聚集动态。结果发现结构不同的斑块形成与Aβ肽的差异性沉积相关, 详细描绘了Aβ病理发生早期事件的全貌。Aβ动力学紊乱可能会激活细胞内信号通路, 包括tau蛋白过度磷酸化通路和促炎通路。Hong等[73]通过MALDI-MSI对组织进行直接分析, 能够确定特定脂质在不同组织中的相对丰度和空间分布。研究结果显示, 在小鼠Aβ斑块最先形成的脑部区域, 脂质分布发生了变化, 这一发现为AD病理机制解释提供了新的见解。

MSI技术结合脂质组学的研究为解析AD脑内脂

Table 1 Comparison of mass spectrometry imaging techniques in spatially resolved metabolomics. MSI: Mass spectrometry imaging; FFPE: Formalin-fixed paraffin-embedded

MSI technology	MALDI-MSI	DESI-MSI	AFADESI-MSI
Ionization mode	MALDI	DESI	AFADESI
Ionization principle	1. The matrix absorbs laser energy 2. Energy transfer promotes the ionization of the sample 3. The spatial distribution information of the sample is preserved	1. The sprayed droplets interact with the sample surface and desorb sample molecules 2. Charge transfer occurs within the droplets, promoting the ionization of the sample 3. The spatial distribution information of the sample is preserved	1. High-speed charged spray droplets impact the sample surface 2. Charge transfer and ionization occur within the droplets 3. The spatial distribution information of the sample is preserved
Types of MSI	Vacuum environment	Atmospheric pressure	Atmospheric pressure
Sample preparation	1. Cryopreserve frozen tissue; dewax and rehydrate FFPE tissue 2. Uniformly deposit matrix onto the surface of tissue sections (a critical step)	Cryopreserve frozen tissue; dewax and rehydrate FFPE tissue	Cryopreserve frozen tissue; dewax and rehydrate FFPE tissue
Spatial resolution	Maximum spatial resolution: 0.6 μm Typical range for research applications: 5−150 μm	Maximum spatial resolution: 7 μm Typical range for research applications: 150−200 μm	Typical range for research applications: 50−100 μm
Main advantage	High spatial resolution	High throughput and fast detection speed	High sensitivity and wide coverage for metabolite detection
Main limitation	Requires complex sample preparation and vacuum conditions	Low sensitivity and low spatial resolution	Low spatial resolution
Ref.	[61−63]	[64−66]	[67]

质代谢的时空特征及潜在标志物筛选提供了关键线索。Li 等[74]在 AD 小鼠与野生型小鼠海马体、丘脑的脂质组学差异及相关代谢通路机制的研究过程中, 发现了 88 种具有年龄和区域特异性改变的脂质, 其中二酰甘油有望成为 AD 的早期诊断生物标志物。Huang 等[75]在利用 DESI-MSI 对 AD 小鼠大脑脂质组成的空间局部差异和整体差异进行全面表征时, 发现小鼠 Aβ 斑块周围的溶血磷脂、双 (单酰基甘油) 磷酸酯和磷脂酰甘油随年龄增长而增加, 因此研究得出“斑块富集模块脂质可作为 Aβ 斑块进展指标”的结论。

多奈哌齐 (donepezil, DNP) 是临床治疗 AD 的常用一线药物, 也是 AD 创新药物研发中广泛采用的阳性对照药, 但其在脑内的空间分布特征尚未明确。Shanta 等[76]开发出由 3-羟基香豆素与 6-氮杂-2-硫代胸腺嘧啶组成的新型复合基质, 在小鼠完整组织切片上完成了 DNP 的药物分布成像。成像质谱分析结果清晰显示, 原型 DNP 在大脑皮质区域高度富集。MSI 技术的持续发展, 也为中药防治 AD 的研究提供了全新的技术视角与研究手段。Fan 等[77]通过空间代谢组学鉴定出 28 个与 AD 神经炎症、递质失衡等病理环节相关的生物标志物, 人参−五味子药对可调控其中 22 个; 该药对小分子组分调控 19 个标志物、大分子组分影响 14 个, 9 种小分子成分为其核心药效物质。Chen 等[78]利用 MALDI-MSI 研究发现, 远志提取物干预可显著逆转小鼠脑内脑区特异性的代谢紊乱, 改善五个脑区间 (大脑皮层、海马体、胼胝体、丘脑和下丘脑) 的代谢协同性。以上研究表明结合空间代谢组学与网络药理学等多维度技术手段, 能够从系统层面揭示 AD 发生发展中的代谢网络扰动规律及中药复方的干预机制。

2.2 帕金森病

PD 是临床常见的 CNS 退行性疾病, 其典型病理特征表现为中脑黑质致密部多巴胺能神经元的进行性丢失, 以及 α-突触核蛋白异常聚集形成路易小体[79,80], 当前临床治疗以对症干预为主[81,82], 尚无根治手段。空间代谢组学技术可有效围绕 PD 的发病机制开展病理机制、生物标志物发现及药物研究。

前蛋白水解酶体 (prosaposin, PSAP) 可调节糖鞘脂代谢, 其基因变异与 PD 存在关联。但其中病理机制并不明确, He 等[83]利用 MALDI-MSI 技术在空间层面上对脂质组的变化特征进行了分析, 结果表明, PSAP 可能在维持多巴胺能神经元脂质稳态中发挥关键作用 (该稳态在 PD 中存在失调), 同时对实验性帕金森病综合征具有拮抗效应。1-甲基-4-苯基-1,2,3,6-四氢吡啶 (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, MPTP) 在脑内代谢为神经毒素 1-甲基-4-苯基吡啶离子 (methyl-phenyl-pyridinium, MPP^+) 后, 会破坏人类及非人灵长类动物黑质致密部的多巴胺能神经元, 进而引发永久性帕金森病样症状。然而, MPTP 诱导的帕金森病综合征背后完整的分子病理机制仍未被充分阐明。Kaya 等[84]采用 MALDI-MSI 技术, 对 MPTP 损

伤模型及对照组恒河猴的脑冠状切片中多种甘油磷脂和鞘脂进行了全面成像分析。研究结果表明, MPTP损伤恒河猴脑内存在区域特异性的硫苷脂代谢失调。MPTP诱导病理模型中长链羟基化硫苷脂的耗竭, 提示在这些病理相关脑区存在氧化应激及少突胶质细胞/髓鞘损伤。

富含亮氨酸重复序列激酶2 (leucine-rich repeat kinase 2, LRRK2) 的致病性变异会使其激酶活性增强, 目前临床上将LRRK2激酶抑制列为帕金森病的潜在治疗方向展开探索。Maloney等[85]通过MALDI-MSI技术与液相色谱–串联质谱法 (liquid chromatography-tandem mass spectrometry, LC-MS/MS) 结合的研究发现, LRRK2激酶活性可通过组织特异性机制调控溶酶体相关脂质的水平, 其抑制剂能够改善PD相关的溶酶体功能障碍, 而糖鞘脂有望成为脑脊液中LRRK2活性的潜在生物标志物。

神经炎症、氧化应激和线粒体功能障碍是PD患者出现运动功能障碍和多巴胺能神经元损伤的重要潜在致病机制。Wu等[86]通过MALDI-MSI技术, 结合生化分析和行为学测试证实了淫羊藿素可通过抑制NOD样受体家族含pyrin结构域蛋白3炎症小体活性并稳定线粒体功能, 从而发挥改善PD的作用。左旋多巴 (*L*-3,4-dihydroxyphenylalanine, *L*-DOPA) 是治疗PD的有效药物, 但长期使用会引发异常不自主运动 (*L*-DOPA-induced dyskinesia, LID), 其病理机制尚未明确。Fridjonsdottir等[87]采用MALDI-MSI技术对LID和未出现LID灵长类动物大脑中*L*-DOPA的分布及单胺能通路特征进行了分析。结果表明, LID动物体内, *L*-DOPA水平显著升高, 导致纹状体外脑区结构中的多巴胺及其代谢产物含量增加; 此外, *L*-DOPA的主要代谢产物3-氧-甲基多巴在LID模型动物中同样呈显著高表达, 这表明*L*-DOPA代谢过程存在异常调控。

2.3 缺血性脑卒中

IS因脑局部供血障碍致脑组织缺血缺氧坏死, 表现为神经功能缺损, 具有高发病率、高复发率、高致残率、高死亡率特点, 存活者多遗留神经功能障碍[88,89]。空间代谢组学可定位组织代谢物分布, 助力其研究。

了解IS大脑内脂质的空间变化, 对于阐明IS进展及治疗反应的潜在机制至关重要。Mulder等[90]以MALDI-MSI和SIMS-MSI技术, 在IS转基因小鼠模型中, 对不同时间点的脑内梗死核心、半暗带及健康组织脂质谱展开分析, 揭示了脂质代谢紊乱与离子失衡的病理机制, 证实脂质谱变化可作为区分梗死核心与半暗带的分子标志, 为早期生物标志物开发提供了思路。在此基础上, Li等[91]进一步运用MALDI-MSI技术结合拟靶向脂质组学, 将研究时间窗前移至IS早期, 发现缺血脑区在梗死可见前1小时即出现显著脂质改变, 且脂质谱变化较传统组织病理学方法更为敏感, 其时空模式与梗死扩展高度相关。这一进展不仅将脂质标志物的发现时间窗口大幅提前, 更通过技术整合为解析早期缺血性脑损伤机制提供了更全面的平台, 推动了从生物标志物发现到疾病分子机制深入理解的研究递进。

缺血区域的代谢失调已被越来越多地认为是IS发病机制的促成因素之一。桃红四物汤 (Taohong Siwu decoction, THSWD) 是一种用于活血化瘀的中药制剂, 常被用于IS的治疗。然而, THSWD在缺血性脑卒中治疗中发挥疗效的潜在代谢调控机制, 目前仍大多未被阐明。针对此问题, Wang等[92]运用DESI-MSI技术, 探究了THSWD对缺血脑区内源性代谢物空间分布及水平的调节作用, 发现缺血损伤后30种代谢物显著失调, THSWD可通过恢复能量代谢、改善神经递质代谢和修复多胺代谢等途径发挥治疗作用。Zhang等[93]运用DESI-MSI聚焦脑内脂质这一特定代谢范畴探讨THSWD的治疗机制, 探究药物对脑内脂质紊乱的空间调节效应。以上研究内容进一步验证了DESI-MSI技术在药物干预效果呈现中的有效性。

2.4 抑郁症

抑郁症是常见精神障碍, 以心境低落、思维迟缓等为特征[94], 发病与神经、免疫等系统紊乱相关, 全球患者已超3.1亿[95], 代谢物作为上游基因表达和蛋白质调控网络的产物, 在抑郁症生理和病理生理过程中发挥着关键作用。在传统代谢组学研究中, 难以实现代谢物的空间定位, 这制约了研究人员对脑代谢组学的进一步分析。空间代谢组学通过MSI技术精准解析代谢物空间分布, 为抑郁症研究突破提供新路径。

抑郁症与多个脑区的病理改变及代谢异常相关。全面理解抑郁症病理机制的关键在于, 对全脑区的内源性分子进行同步、全面且原位的检测, Song等[96]基于DESI-MSI技术, 利用特征性脂质分子实现小鼠脑区分类, 同时对小鼠脑组织样本中的代谢物进行检测。结果显示, 特征性脂质分子可清晰区分小鼠大脑的各个细分脑区, 首次发现了皮质区存在能量代谢特征性改变, 纹状体存在嘌呤代谢特征性改变。Sheng等[97]则针对特定类型抑郁症产后抑郁 (postpartum depression, PPD), 结合MSI与靶向代谢组学分析发现, 中央杏仁核的前列腺素D2 (prostaglandin D2, PGD2) 下调是PPD小鼠最显著代谢变化, 进一步研究证实了脂钙蛋白型前列腺素D合酶/PGD2信号异常通过抑制Src磷酸化诱导星形胶质细胞萎缩进而介导PPD, 深化了抑郁症病理

机制认知。Minsi等[98]采用机器学习辅助的MALDI-MSI, 在抑郁相关干眼症大鼠海马组织及齿状回亚区检测到120多种代谢物, 发现3-氧-磺基半乳糖神经酰胺、磷脂酰肌醇等脂质及一磷酸腺苷、二磷酸腺苷等嘌呤代谢物可能为潜在生物标志物, 且胞苷二磷酸−乙醇胺减少与磷脂酰甘油、三磷酸鸟苷等增加与疾病发展相关, 揭示了海马亚区代谢差异在抑郁相关疾病中的作用, 丰富了抑郁症及其并发症的代谢调控研究。

MSI是实现未标记药物及其代谢物空间分布可视化绘制的强大技术手段, 可应用于药物递送效果评估、作用机制阐释及潜在毒性识别等研究。Khalil等[99]研究了抗抑郁药度洛西汀的空间分布检测; 该药为临床常用处方药物, 但其引发肝损伤、持续性头痛等常见不良反应的作用机制尚未完全明确。研究采用MALDI-MSI技术, 检测了度洛西汀及其主要代谢物在小鼠脑、肝、肾、脾这四个与药物疗效发挥或毒性产生密切相关的器官中的分布特征。结果显示, 度洛西汀及其代谢物在上述所有组织中均非均匀分布, 这一特征与药物的疗效和毒性均存在关联。氯胺酮是一种新型、快速且有效的抗抑郁治疗手段, 然而, 其可能产生的解离效应、感觉改变、滥用风险, 以及无法准确判断患者是否对氯胺酮产生显著反应等问题, 限制了它在临床上的应用。深入探究氯胺酮的抗抑郁机制, 将有助于其安全且实际的应用。Liu等[100]聚焦于其作用机制探索, 通过AFADESI-MSI研究发现小鼠经*S*-氯胺酮注射后, 全脑范围内以甘油磷脂代谢的改变为主, 而鞘脂代谢的变化则主要集中在苍白球区域, 阐明了*S*-氯胺酮通过调控特定脑区膜脂代谢发挥抗抑郁效应的机制, 为抑郁症治疗提供了新的机制参考。

2.5 脑肿瘤

脑肿瘤是CNS常见病变, 其中胶质母细胞瘤(glioblastoma, GBM) 作为原发恶性肿瘤, 以高异质性、强浸润性和差预后为特征[101-104], 其代谢紊乱与微环境异常是疾病进展关键[105], 现有诊疗因难以精准识别病灶及药物分布不均面临挑战。空间代谢组学为解决这些问题提供新视角。Lu等[106]采用MALDI-MSI比较不同基质, 确定了脑肿瘤代谢物检测的最优方案, 为后续脑肿瘤相关病理机制研究与生物标志物挖掘提供了关键技术支撑; Hendriks等[107]应用MALDI-MSI等技术, 聚焦异柠檬酸脱氢酶野生型GBM, 通过空间代谢组研究其总体生存预测, 成功识别出短期与长期生存者的脂质组学关键鉴别特征, 进一步探索了GBM生存相关的病理机制并挖掘了脂质生物标志物; Angerstein等[108]同样借助MALDI-MSI技术, 深入分析GBM组织中*N*-糖链的空间分布, 不仅揭示了GBM与少突胶质细胞瘤的糖基化差异, 还探索了替莫唑胺敏感/耐药相关的*N*-糖标志物及其调控基因, 从糖基化异常这一维度补充了GBM的病理机制研究并丰富了其分子标志物类型; 基于上述对GBM病理机制与分子特征的系统探索, Liu等[109]利用AFADESI-MSI技术转向药物研究, 探究了金霉素A对GBM糖、谷氨酸及脂质代谢的重塑作用, 以及其对氧化应激的调控效果, 为GBM的治疗提供了新的作用靶点与潜在策略; 此外, Gold等[110]则将研究范围从GBM扩展到另一类脑肿瘤, 通过MALDI-MSI技术研究音猬因子 (SHH) 亚型髓母细胞瘤的异质性, 揭示了其与小脑颗粒神经元发育阶段的关联, 进一步完善了脑肿瘤异质性病理机制的研究体系。

此外, 亨廷顿舞蹈症 (Huntington's disease, HD) 也是临床常见CNS常染色体显性遗传神经退行性疾病[111]。其典型表现为慢性进行性舞蹈样不自主运动, 伴认知功能减退与情绪行为障碍[112], 最终导致患者丧失行动、言语及吞咽能力而死亡。目前尚无特效治疗手段[113], 仅通过药物、康复及心理干预对症支持, 无法逆转神经元损伤或延缓病程进展。空间代谢组学为HD研究提供了新视角, 可定位脑内不同区域的代谢紊乱。空间代谢组学在CNS疾病中的更多应用详见表2[16,114-126]。

3 总结与展望

以MSI技术为核心的空间代谢组学以高灵敏、高分辨、高覆盖、高特异性、无需标记等优势在生物组织分子表征领域展现出巨大潜力, 尤其在异质性人脑组织的比较研究中具有不可替代的价值, 在CNS疾病包括AD、PD、IS、抑郁症及脑肿瘤等研究中应用日益增多, 对疾病机制解析、特异性生物标志物筛选与验证以及药物研发提供了全新的技术支撑。

尽管空间代谢组学在上述研究中取得了显著进展, 但仍存在诸多亟待解决的不足, 从技术层面看, 现有三种MSI技术在疾病研究时均存在局限性, MALDI-MSI存在基质干扰问题, DESI-MSI与AFADESI-MSI的空间分辨率有待提升, 三种技术定量准确性不足且不同技术间的结果可比性较差, 代谢物数据库的不完善也限制了未知代谢物的鉴定效率; 未来, 空间代谢组学发展在技术层面应重点攻关离子源、检测器等核心部件的性能迭代, 如开发MALDI-MSI的无基质电离技术[127]、优化基质配方, 减少离子抑制与背景干扰[128]; 升级DESI-MSI与AFADESI-MSI的离子源聚焦系统[129]以提升空间分辨率、增强信号强度与灵敏度检测低丰度分子并改善实验重复性与稳定性, 降低操作依赖性, 突破单细胞空间代谢组学技术瓶颈, 实现单细胞水平代谢特征的精准解析, 精准捕捉细胞异质性, 实现脑部

物质成像的高分辨率、高灵敏度及小分子成像的重大突破。与此同时, 开发模块化MSI平台以支持不同电离技术切换, 统一离子化参数与检测标准, 减少技术间系统误差, 为结果可比性奠定硬件基础。软件数据处理端需重点开发高效算法模型, 优化代谢物注释流程, 整合临床样本、动物模型、细胞系的CNS疾病特异性代谢物库数据, 构建“空间–结构–功能”三位一体的数据库。

Table 2 Application of spatial metabolomics technology in central nervous system diseases. AD: Alzheimer's disease; PD: Parkinson's disease; IS: Ischemic stroke; GBM: Glioblastoma; HD: Huntington's disease; Aβ: β-Amyloid protein; *L*-DOPA: *L*-3,4-Dihydroxyphenylalanine; 5-HT: 5-Hydroxytryptamine; CQDs: Carbon quantum dots; NG-R1: Notoginsenoside R1

Disease	MSI technology	Matrix treatment	Research content	Conclusion	Reference
AD	MALDI	2-Mercaptobenzothiazole	Reveal the spatial changes of AD-related lipid species and correlate lipid spatial changes with AD pathology	Lipid changes in specific brain regions of AD mice indicate neuroprotective adaptive responses that improve neurotransmission, alleviate myelin abnormalities, and reduce astrocyte-related neuroinflammation, supporting a theoretical basis for lipid-targeted AD therapy	[114]
	MALDI	*N*-(1-Naphthyl) ethylenediamine dihydrochloride; α-cyano-4-hydroxycinnamic acid	Reveal brain region-specific metabolic disturbances in AD and their association with neurodegeneration	Metabolic disturbances are confirmed to be important drivers of neurodegeneration in AD; glycogen is significantly elevated in the allocortical regions of AD mice and can serve as a potential marker for AD-related metabolic dysregulation	[115]
	AFADESI	/	To investigate the spatial distribution changes of metabolic networks and microregion-specific metabolic disorders in the brain of AD models	The scopolamine-induced AD model exhibits metabolic disturbances in brain microregions, with the pons and cerebral cortex being most significantly affected, and neurotransmitter network disorder as the core; a total of 47 differential metabolites were identified	[16]
	MALDI	4-Aminoquinoline-3-carboxamide	Spatial distribution and region-specific changes of small molecule metabolites in the brain, as well as spatial distribution and content differences of lipids in the brain	In key brain regions of AD mice, tricarboxylic acid cycle imbalance, nucleotide accumulation, and lipid abnormalities exhibit a specific spatial distribution. Some metabolites in the brain and serum are simultaneously elevated, while others show opposite changes; some lipids can be regarded as potential biomarkers for AD	[116]
	MALDI	9-Aminoanthracene	To investigate the correlation between the spatial distribution of metabolites and the pathological mechanism in the brain of early-stage AD mice using spatial metabolomics	It is confirmed that abnormal fatty acid metabolism in astrocytes is a key early feature of AD, and it participates in the pathological progression of AD synergistically with metabolic disturbances in brain regions and decreased energy metabolism	[117]
PD	MALDI	Fluoromethylpyridinium	To reveal the spatial distribution changes of neurotransmitters and their metabolites in brain regions of PD, as well as the metabolic mechanism of the drug *L*-DOPA	The main characteristics of neurotransmitter imbalance in the PD model are damage to the dopaminergic system, abnormalities in the serotonergic system, and a significant depletion of norepinephrine in the ipsilateral cortex of injured rats. *L*-DOPA and its deuterated derivative (*L*-DOPA-d3) can be converted into metabolites such as dopamine-d3 and 3-methoxytyramine-d3 in the brain. Meanwhile, *L*-DOPA treatment increases the level of γ-aminobutyric acid in the ipsilateral striatum of the injured side	[118]
	AFADESI	/	Spatial metabolomics analysis reveals region-specific neurotoxicity-related metabolic alterations in mouse brain induced by CQDs	The neurotoxicity biomarkers of CQDs mainly include amino compounds, lipids and lipid-like molecules. These substances are involved in pathways such as arginine-proline metabolism and unsaturated fatty acid biosynthesis, regulate the activity of related metabolic enzymes, and further induce neuroinflammation, organelle damage, oxidative stress, and multiple types of programmed cell death	[119]

Continued

Disease	MSI technology	Matrix treatment	Research content	Conclusion	Reference
IS	MALDI	*α*-Cyano-4-hydroxycinnamic acid	To investigate the spatial metabolic disorders of amine metabolites in an IS model, as well as the regulatory effects of edaravone and ginaton administered alone and in combination	Marked metabolic disturbances occurred in the rat cerebral cortex and striatum; combination treatment significantly alleviated ischemic brain injury and corrected the spatial metabolic disorders of amine metabolites	[120]
	MALDI	1,5-Diaminonaphthalene dihydrochloride	To investigate the regulatory effect of NG-R1 on metabolism in the brain of IS rats	IS causes multiple pathological changes. Metabolic abnormalities in the striatum and hippocampus underlie brain injury by impairing metabolism and ionic homeostasis, and these metabolic disturbances further exacerbate brain damage. The neuroprotective effect of NG-R1 is comparable to that of the positive drug *DL*-3-*n*-butylphthalide	[121]
	AFADESI	/	To investigate the distribution characteristics and metabolic regulatory effects of pterostilbene in the brain of rats with cerebral ischemia-reperfusion injury	Pterostilbene can significantly restore cerebral microcirculatory blood flow, reduce cerebral infarct volume, improve neurological function, and alleviate neuronal damage in rats with IS models. Meanwhile, pterostilbene exhibits an extensive and high-abundance distribution pattern in ischemic brain tissue	[122]
GBM	MALDI	9-Aminoacridine hydrochloride monohydrate	Decoding spatial heterogeneity, tumor-host interactions, and metabolome-genome associations in GBM	This study reveals that GBM exhibits regional tumor-host interactions, which can induce spatially specific adaptive transcriptional regulatory programs	[123]
HD	MALDI	/	To investigate the spatiotemporal changes of lipid metabolism in the hippocampus of HD mice and their association with disease pathology	Lipid abnormalities appear as early as 6 weeks before the onset of symptoms in HD mice; these pre-symptomatic lipid changes can serve as early warning biomarkers	[124]
	MALDI	1,5-Diaminonaphthalene	To explore the potential role of lipidomic abnormalities in the neuropathology of HD	The lipid distribution in the caudate nucleus is highly conserved. In HD patients, neuroprotective lipids such as docosahexaenoic acid are decreased, while multiple sphingomyelins and glycerophospholipids containing short monounsaturated acyl chains are locally elevated	[125]
	MALDI	2,5-Dihydroxybenzoic acid	To detect proteomic changes at different stages of disease progression in a mouse model of HD	The pathological mechanisms of HD differ across stages: The early stage involves pathways such as actin cytoskeleton organization, the mild stage focuses on synaptic function-related pathways, and the pathological stage includes neurodegenerative pathways	[126]

从CNS疾病研究层面看, 当前研究多依赖动物模型, 临床样本的研究占比偏低且样本量有限, 难以真实反映人类疾病的代谢特征, 对常见的CNS疾病的代谢紊乱机制研究多集中于单一疾病的独立分析, 缺乏疾病间共性与特异性代谢通路的系统对比, 筛选出的生物标志物多处于基础研究阶段, 缺乏大样本临床验证且未形成统一的检测标准, 临床转化难度较大, 药物研究中MSI技术多用于药物分布可视化, 对药物代谢产物与疾病代谢网络的相互作用、药物靶点的精准定位等深度解析不足。

不同CNS疾病的病理累及脑区具有特异性: AD的早期核心发病部位为海马体与内嗅皮层, 病变会逐步蔓延至大脑皮层, 上述区域是Aβ斑块沉积、神经纤维缠结形成及神经元丢失的主要发生部位[130,131]; PD的病变核心集中于中脑黑质致密部[132]; IS则以大脑中动脉供血区 (涵盖大脑半球外侧部的额叶、顶叶、颞叶部分区域) 为高发部位[133]等。今后针对上述CNS疾病的特征性发病脑区开展空间代谢组学分析, 可依托患者诱导多能干细胞 (induced pluripotent stem cells, iPSC), 分化生成含血脑屏障 (blood-brain barrier, BBB) 结构的脑类器官、多巴胺能神经元类器官等模型, 精准模拟CNS疾病相关病理微环境 (如淀粉样蛋白沉积、神经

纤维缠结)[134,135], 进而实现类器官内不同区域 (如皮质、海马体) 的精准代谢分析, 实时捕获疾病进展过程中的代谢动态变化。进一步整合脑类器官与微流控灌注系统 (模拟脑部血流动力学特征)[136], 并与空间代谢组学联动, 可实现代谢过程的动态检测, 追踪代谢紊乱的时空演变规律 (如早期能量代谢异常), 评估药物穿透BBB后的空间分布特征与代谢转化效率, 结合代谢网络分析精准预测药物疗效与毒性, 从而降低对动物实验的依赖, 通过空间代谢组学筛选个体化治疗药物, 为精准医疗的实现提供支撑。此外, 在脑部类器官或器官芯片中引入荧光标记的代谢物探针, 结合MSI技术可实现代谢物转运与转化过程的实时可视化, 进一步开发多通道脑部器官芯片阵列, 能够实现大规模药物代谢活性筛选, 显著提升药物研发效率。相信随着MSI技术、CNS相关类器官模型、器官芯片等的不断发展和完善, 空间代谢组学将会在CNS疾病研究中展现出更大的潜力和应用前景。

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