基于离子淌度-质谱技术分析小分子代谢物的研究进展

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摘要:近年来,不同原理的离子淌度技术相继出现,与质谱技术相结合已广泛应用于许多领域。在小分子代谢物分析中,氨基酸的手性识别、聚糖的结构解析、脂质的结构表征和类固醇的分析十分重要,但由于小分子代谢物化学性质迥异,且普遍存在同分异构现象,增加了分析难度。离子淌度-质谱(IM-MS)技术为复杂基质中小分子代谢物的快速分离和分析提供了新思路,根据离子的质荷比、碰撞截面积(CCS)和结构信息,可快速区分、表征小分子代谢物及其同分异构体。本文介绍了离子淌度-质谱(IM-MS)的主要类型及其在小分子代谢物分析中的应用情况和存在的不足,并展望其发展前景。

关键词:离子淌度-质谱(IM-MS);碰撞截面积(CCS);小分子代谢物;同分异构体
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Recent Advances in Small Molecule Metabolites Analysis by Ion Mobility-Mass Spectrometry

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Abstract: Recently, different types of ion mobility techniques have sprung up. Combined with mass spectrometry, the utility of ion mobility spectrometry has been enhanced in metabolomics, natural products, characterization of supramolecular materials, and other research fields. Since small molecule metabolites provide deep insight into the dynamic phenotypes of biological systems and show potential value in disease diagnosis and functional interpretation, in-depth analysis of small molecule metabolites plays a key role in medicine and pharmacy. The potential benefits of ion mobility spectrometry used in chiral recognition of amino acids, structural analysis of glycans, and structural characterization of lipids and steroids have become the specific focus of work. However,

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small molecule metabolites possess a wide variety of chemical properties, ubiquitous isomerism, and various biological functions, so it is difficult to analyze small molecule metabolites comprehensively. On the other hand, small molecule metabolites with low concentrations usually exist in various complex biological matrices, such as plasma, feces, urine, saliva, sweat, infected tissues or exudates, breath, and breast milk, which pose additional challenges to researchers. Over the last few decades, ion mobility-mass spectrometry (IM-MS) has undergone inordinate growth in instrument development and performance, which has opened a new door to rapidly analyze small molecular metabolites in complex biological matrices. Small molecular metabolites and their isomers can be distinguished and characterized in milliseconds by IM-MS that offer high selectivity and three-dimensional information about them, including mass-charge ratio, collision cross section (CCS), and structural information. The collision cross section can be used as an additional identification basis in targeted and untargeted analyses. In this paper, the main commercial IM-MS instruments were briefly covered. An overview of the latest applications in small molecular metabolites was offered. Additionally, the advantages and shortcomings of IM-MS in the analysis of small molecular metabolites were discussed. And the future application of particular and unknown metabolites by IM-MS in the studies on the biological mechanism and precision medicine was prospected.

Key words: ion mobility-mass spectrometry (IM-MS); collision cross section (CCS); small molecule metabolites; isomer

小分子代谢物(SMMs)一般指生物系统中分子质量低于 600 u[1-2],具有特定生理活性或反映机体健康状态的化合物。对 SMMs 的分析有助于更好地理解疾病的发展机制,发现疾病诊断的生物标志物[3]。SMMs 通常存在于生物样品中,涵盖氨基酸、糖类、脂肪酸、脂质和维生素等不同化合物[4]。由于提取技术的不同和物化性质的差异,使多种 SMMs 的同时分析受到限制,而且 SMMs 的鉴定受同分异构体和同量异位素化合物等因素的干扰。样品的定量分析通常需要高灵敏度的分析平台,而生物样品中代谢物的含量较低,不适宜用核磁共振法进行结构表征。色谱分析可获得化合物的保留时间、质荷比、特征碎片等信息,广泛应用于 SMMs 的分析中[6-7],但不适合高通量测试,且许多异构体代谢物的定性问题仍然没有得到解决。质谱技术能够快速、高灵敏度和高选择性地分析化合物,但根据分析物的立体结构进行区分超出了常规质谱分析的范畴,需要第二维度来获取分析物群体的结构异质性[5]。

离子淌度(IMS)是一种毫秒级的气相离子分离技术[8],其核心原理是电场驱动离子在气体阻尼环境中的迁移速率存在差异,通过离子的电荷状态、大小、形状、电荷位置或结构刚度可实现分离[9]。离子迁移谱的研究最早可追溯到 20 世纪初[10-12],然而,直至 20 世纪 60 年代,第一台商品化的离子淌度仪才作为分析仪器问世[13],主要用于毒品等挥发性有机物的痕量检测[14]以及爆炸物[15]、化学战剂[16]和空气污染物[17]的分析。在过去几十年,IMS 经历了快速的发展,其不仅仅是化学战剂和爆炸物的探测器,也成为生物分析的有力工具。为了完成日益复杂的,尤其是超高分辨率(>ca. 200)的测量任务,对仪器分析性能的要求越来越高[18]。

20 世纪 60 年代,为研究气相离子化学开发了离子淌度-质谱(IM-MS)仪[19]。目前,与 IMS 联用的有四极杆质谱、飞行时间质谱、轨道离子阱质谱和离子阱质谱[20]。MS 根据质荷比的不同区分离子,给出分析物的特性和分子组成详细信息。IMS 根据离子通过缓冲气体时迁移率的不同分离离子,从另一个维度使原本难以区分的离子快速分离。MS 和 IM 间存在强大的协同效应,能够提供气相离子的补充信息[22]。然而,测定离子迁移率时,电喷雾溶

剂组成和流速、漂移区温度、溶液浓度和色散电压[21]等因素均会影响结果。因此,在建立分析方法前需要优化仪器参数。

自2006年开发商业IM-MS仪器以来[23],该技术在法医学、环境科学、制药、材料、医学、化学战剂和爆炸物检测等领域得到了广泛应用[24-26]。IM-MS可在不增加分析时间的情况下提高MS检测的选择性[27-28],具有3个主要技术优势:1) IM为样品分析增加了1个分离维度,可增加峰容量和信噪比[29];2) 可提供离子碰撞截面积(CCS)作为分析物识别的额外度量;3) 作为描述化合物结构模型的几何参数,即将离子淌度的测量值(漂移时间或电场强度)转换为CCS测量值以表征气相分析物的化学结构和三维构象。近年来,IM-MS在天然产物[30-31]、微生物[32]、糖类[33-35]、脂质组学[36-38]、蛋白质组学[39-40]、食品[41]和环境样品[42]检测方面受到关注。

本综述将主要介绍IM-MS在小分子代谢物研究中取得的进展,展望其在生命科学研究中的应用前景。希望为研究人员建立小分子代谢物离子淌度-质谱分析方法提供参考。

1　离子淌度-质谱技术

1.1　仪器

商品化的IMS仪器包括漂移管离子淌度(DTIMS)[43]、行波离子淌度(TWIMS)[44]、高场不对称波形离子淌度(FAIMS)[45]、捕集离子淌度(TIMS)[46]、环形离子淌度(cIMS)[47]、无损离子操纵淌度(SLIM)[48]。此外,未商品化但分辨率较高的仪器(如U形离子淌度(UMA)[49])也有所使用。TIMS、cIMS、SLIM和UMA的分辨率均大于200,是高分辨离子淌度仪,详细情况列于表1。

表1　常用的离子淌度-质谱仪信息

Table 1　Information of commonly used ion mobility mass spectrometer

离子淌度仪 IMS	商品化仪器 Commercial instrument	上市年份 Year of listing	兼容质谱仪 Compatible MS	分辨率 Resolution	碎片离子分离 Separation of fragment ion
DTIMS	IM Q TOF(Agilent)	2014	TOF	60～80	—
TWIMS	SYNAPT HDMS(Waters)	2006	TOF	40～50	可获得
FAIMS	Selex ION(AB Sciex)	2012	Q-Trap,TOF	40	—
TIMS	TIMS TOF(Bruker)	2016	TOF	200～400	—
cIMS	Cyclic IMS(Waters)	2019	TOF	80～750	可获得
SLIM	SLIM(MOBILion Systems)	2014	Q-TOF	340±10	可获得
UMA	—	—	Q-q-Q, Q-TOF	180～350	—

常见的商品化离子淌度仪类型示于图1。根据分离模式,IMS可分为时间扩散型、空间扩散型、限制和选择性释放型[50]。时间扩散型离子淌度中的所有离子沿类似的路径漂移,产生到达时间谱,如DTIMS和TWIMS。空间扩散型离子淌度中的离子根据迁移率的差异沿不同漂移路径分离,但在时间上没有显著的色散,如DMA和FAIMS。离子限制和释放型的离子淌度中,将离子捕获在加压区域内,并根据迁移率的差异选择性地喷射离子,如TIMS。

1.2　离子化技术

离子淌度以气相离子的形式分离化合物,选择适宜的离子化技术对待测物分析至关重要。为使IM-MS适用于检测不同极性分析物,将不同离子化机理的离子源与IMS相结合,列于表2。对于小分子代谢物的分析,电喷雾电离(ESI)是使用最广泛的电离源,主要电离生物基质中不同的非挥发性化合物,如氨基酸、脂肪酸、多肽。虽然存在基质抑制效应,但ESI仍适用于大多数小分子代谢物的电离。基于IM-MS的质谱成像研究中,基质辅助激光

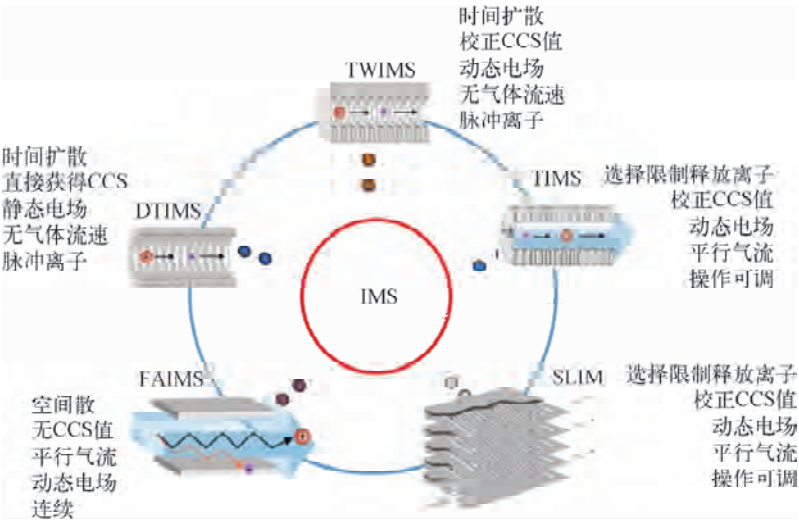


图 1 常见的商品化离子淌度仪类型

Fig. 1 Common commercial instruments of ion mobility spectrometry

解吸电离源(MALDI)使用最广泛。此外,基于电喷雾原理的敞开式离子化技术,如解吸电喷雾电离(DESI)、激光烧蚀电喷雾电离(LAESI)也常用于电离固体样品。

表 2 离子淌度-质谱中使用的离子化技术

Table 2 Ionization techniques used in ion mobility-mass spectrometry

离子化技术 Ionization technique	离子淌度-质谱 IM-MS	分析物 Analyte	参考文献 Reference
ESI	TWMS-MS	多肽	[51]
Nano-ESI	TWMS-MS	脂质	[52]
DESI	DTIMS-MS	蛋白质	[53]
LAESI	cIMS-MS	蛋白质	[54]
MALDI	TIMS-MS	甾醇	[55]

1.3 离子碰撞截面积测量

简单来说,CCS 是对气相离子大小的标准化测量、表征,通常以 Å^2 表示。使用均匀电场 IMS 技术时,CCS 值可以直接由漂移时间得出[56]。如在 DTIMS 中,离子在恒定电场下通过中性气体时,由于离子与缓冲气体发生碰撞,迁移速率降低,质荷比相同但三维结构不同的离子在缓冲气体中的迁移速率不同,离子松散结构将使其具有更多与气体碰撞的机会。因此,相比于紧凑结构,松散结构的离子穿过漂移区的时间将更长。此外,DTIMS 测量的漂移时间包括离子通过漂移管、漂移管后离子光学和飞行管的时间。为测量离子迁移率 K,将离子注入有恒定电场 E、长度 L 的漂移管中,按式(1)测量离子到达探测器所需的漂移时间 t_d。

$$t_d = \frac{L}{KE} \tag{1}$$

由于 DTIM-MS 中气体压力和电子元件的精确控制,使绝对碰撞截面的测量具有高通量和高精度(超过 0.5%),研究人员建立了许多基于氮气氛围的碰撞截面数据库[57-60]。根据 Mason-Schamp 方程[61],通过记录的离子漂移时间计算 CCS 值(Ω),示于式(2)。

$$\Omega = \frac{3ze}{16N}\left(\frac{2\pi}{\mu k_B T}\right)^{1/2}\frac{1}{K_0} \tag{2}$$

其中,K_0 为标准状态(温度、压力)下的迁移率,z 为离子的价态,e 为元电荷,N 为漂移气体的密度,μ 为离子-中性漂移气的折合质量,T 为气体温度,k_B 为玻尔兹曼常数。CCS 值计算软件有 MOBCAL、IMoS 和 hpccs,其中前两者使用较多[62]。计算的 CCS 值为理论值,通过比较 $CCS_{实测}$ 与 $CCS_{理论}$ 对化合物进行定性分析。此外,当使用非均匀电场技术(如 TWIMS)时,由于离子的速度和运动路径不是恒定的,漂移时间与迁移率的倒数不成正比。为了获得非均匀场 IMS 技术的 CCS,可以在相同的实验条件下测量已知 CCS 的校准离子,以计算分析物的 CCS[63]。在最新的 TW-IMS-MS 系统中,校准

步骤已实现完全自动化。常见的离子淌度CCS值的获得情况列于表3。

表3　CCS值的获得情况

Table 3　Acquisition of CCS value

仪器 Instrument	获得方式 Acquisition method
DTIMS	直接获得
TWIMS	校正获得
TIMS	校正获得
FAIMS	不可获得
cIMS	校正获得

2　离子淌度-质谱在小分子代谢物分析中的应用

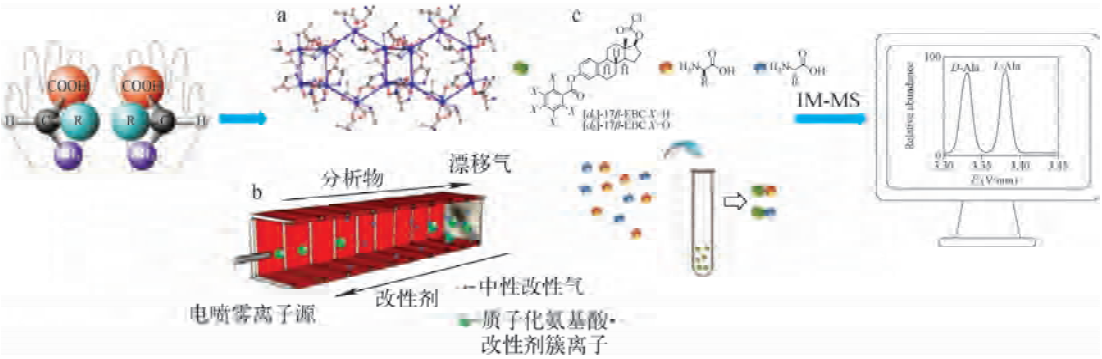
2.1　氨基酸

氨基酸(AAs)是蛋白质的主要组成部分,也是基因表达的调节器及几种激素和神经递质的前体[64]。许多蛋白质氨基酸具有次级代谢作用,例如蛋氨酸可诱发胆固醇合成增强[65],谷氨酰胺可在机体代谢中维持pH值稳态[66]。生物样品中微量游离氨基酸的分析在生物技术和新生儿筛查等领域具有重要意义[67]。IM-MS可完成快速地分离、分析,实现高通量测试。

氨基酸结构中含有—NH_2和—COOH,在ESI电离模式下,分子结构中存在2个质子化位点,即被质子化的—NH_2(氨基质子化离子)和被质子化的—COOH(羧基质子化离子)。基于此,郭寅龙课题组[68]采用IM-MS/MS技术研究了电喷雾电离下亮氨酸和异亮氨酸的电离行为。在IM-MS二维谱图中,由一级质谱图发现二者$[M+H]^+$的质荷比相同,无法区分;由离子淌度图发现二者的漂移时间不同,可通过计算2种质子化离子的CCS值进行区分,并评估氨基酸与其原单体之间的定量关系。结果表明,羧基质子化离子的丰度与氨基酸浓度成正比,而氨基质子化离子的丰度没有相同的趋势。因此,电离模式不仅会影响亮氨酸和异亮氨酸的原聚体形式,而且影响其定量关系。

由于原子的空间排列不同,氨基酸具有手性对映体,即右旋(*D*)或左旋(*L*)对映体。虽然对映体具有几乎相同的结构,但其生物功能不同[69]。此外,氨基酸手性识别在手性生物标志物的诊断和预后中起着至关重要的作用[70]。根据Pirkle法则[71],识别手性氨基酸时需将手性选择分子与对映体络合形成非对映体络合物,以有利于手性氨基酸的分离[72],示于图2。

氨基酸是手性配体,对高价金属离子中心具有较强的亲和力。氨基酸的N和O原子与各种金属离子的螯合能力有助于形成复杂结构[73]。研究人员采用手性氨基酸与二价金属络合,形成金属结合三聚体来分离手性氨基酸[74-75],但该方法需形成相对较大的三聚体,且要优化氨基酸、金属离子和手性选择器之间的浓度比[76]。此外,在漂移气中掺入手性改性剂,其分子离子团簇会产生不同的离子迁移率,以实现手性氨基酸的分离[77],但这种方法需较高的氨基酸浓度。因此,新型的非金属手性选择器的研究成为热点[78]。



注:a. 金属离子;b. 手性改性剂;c. 非金属手性选择器

图2　离子淌度-质谱识别手性氨基酸

Fig. 2　Recognition of chiral amino acid by ion mobility-mass spectrometry

唐科奇课题组[79]利用寡糖作为手性选择剂,采用 TIMS-MS 鉴别了 21 种手性氨基酸。此外,具有手性的环糊精[80]可与氨基酸形成主客体非共价复合物,通过 SLIM 分离,可实现氨基酸对映异构体的高灵敏度检测。IM-MS 与化学衍生化结合也是识别手性氨基酸常用的分析策略,Baker 等[81]采用茴二氧基硫酰氯衍生手性氨基酸形成非对映异构体,并通过 TIMS 分离完成 *D*/*L*-氨基酸的手性鉴别,总分析时间 15 min,衍生化处理使分析周期延长。Karst 等[82]设计了一种手性衍生氨基酸结合 TIMS-MS 自动分析方法,将带有自动进样器的色谱系统与(*S*)-氯化萘普生在线衍生手性氨基酸,衍生物直接引入 ESI-TIMS-MS 系统,分析周期控制在 3 min,可实现高通量、自动化分析。郭寅龙课题组[83]开发了 d_0/d_5-雌二醇-3-苯甲酸-17β-氯甲酸酯(d_0/d_5-17β-EBC)手性选择剂,对氨基酸具有高反应性和良好的对映体分辨率。在 IM-MS 分析之前,使用单一手性选择剂 17β-EBC 对氨基酸进行快速、简单的化学衍生化处理,一次分析周期中,19 个手性蛋白源氨基酸均获得了良好的对映体分离(约 2 s)。同时,利用 d_0/d_5-17β-EBC 建立了对映体过量的线性校准曲线,在 nmol 范围内,测量低至 0.5%的对映体比值。17β-EBC 已成功用于研究肽类药物中氨基酸的绝对构型,并检测复杂生物样品中的微量 D-AAs。d_0/d_5-17β-EBC 可能有助于在肽类药物质量控制和发现手性疾病生物标志物方面的研究。

2.2 多肽

多肽在生物体的信号传导、医疗诊断和治疗方面具有重要作用,识别和定位多肽异构体有助于理解其功能。LC-MS 能够识别许多常见的翻译后修饰多肽,但基于质谱技术的多肽异构体或多肽外消旋体的识别仍不清晰。IM-MS 在确定肽结构、研究神经立体异构和受体、分析肽复合物混合物方面得到广泛应用[84]。Dittmar 等[85]采用 TIMS-Q TOF MS 进行靶向肽定量方法研究,在 30 min 的液相色谱分离过程中检测到约 200 个肽,检测并量化了添加在 HeLa 细胞提取物中的合成肽。

β-淀粉样蛋白(Aβ)积累是阿尔茨海默病的标志之一[51],翻译后修饰的立体异构化 Aβ 肽具有相同的元素组成和相似的物理化学性质,准确分析生成的立体异构体具有挑战性。Roberts等[86]采用 LC-IM-MS 表征散发性阿尔茨海默病大脑颞叶皮质中最常见的异构化淀粉样 b 肽,并对淀粉样蛋白 b 肽的 N 端进行定量评估。结果表明,N 端的天冬氨酸(Asp-1 和 Asp-7)超过 80%发生异构化。另外,IM-MS 能够区分单残基的异构体。Smith 课题组[87]利用 SLIM-MS 结合蛇形超长路径的方法,快速解析异构化和外消旋 *L*-天冬氨酸残基的β-淀粉样胰蛋白酶肽的差向异构体(约 1 s)。为深入了解阿尔茨海默病药物靶点,李灵军等[88]研究了 Aβ 肽的手性效应,为表位区域特异性、手性调节的 Aβ 片段自组装及其对受体识别的潜在影响提供了进一步的结构和分子证据,该结果可能为 Aβ 表位区域对外部刺激的特异性反应提供补充见解。

此外,药物-抗体比率是评估抗体-药物复合物的疗效、安全性和选择性的关键指标,但药物结合的异质性以及单克隆抗体中可能存在的大量翻译后修饰难以表征。采用 IM-MS 可以快速确定抗体上结合药物的平均数量,更好地了解其潜在毒性和效力[89]。

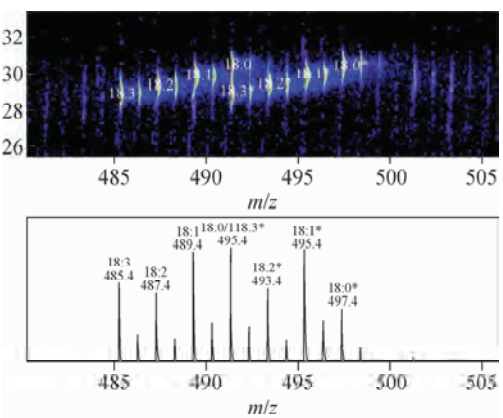
2.3 脂质

脂质作为细胞膜、能量储存和信号分子的成分,在哺乳动物的生物功能中发挥着多重作用。脂质种类数量巨大且多样,不饱和脂肪酰链位置(sn-1、sn-2 或 sn-3)、双键的位置和方向(顺式或反式)以及官能团立体化学(*R* 与 *S*)与特定脂质生物学基质与疾病相关[90]。因此,阐明脂质异构体的结构对探索其功能至关重要。基于质谱法的脂质分析将脂质类型识别和脂质结构信息结合起来以提高表征能力[91],臭氧诱导解析[92-94]、紫外光解离[95]、低温等离子体[96]、Paterno-Buchi 反应[97]等方法均被应用于不饱和脂肪酸双键位置分析中。相比于以上方法,IM-MS 可直接、快速地分离气相的脂质离子,成为复杂生物样品中脂质异构体高通量分析的有力工具。

在生物体内,脂肪酸通常与甘油三酯和磷脂相结合,或以游离酸的形式存在[98]。郭寅龙课题组[99]采用 ESI-IM-MS 研究了 18 种脂肪酸的离子迁移率和碰撞截面积。结果表明,饱

和脂肪酸、单不饱和脂肪酸、多不饱和脂肪酸以及顺/反异构体中脂肪族的尾链长度对漂移分化影响较大,而双键的数目对漂移分化影响较小。对于含有共轭双键的不饱和脂肪酸,如亚油酸和油酸,瑕瑜课题组[100]采用 Paternò-Bùchi 反应结合 TIMS-MS 分析了不饱和脂肪酸的顺、反异构体。

采用 IM-MS 直接进样时,不经色谱直接快速完成分离,其潜在缺陷是离子抑制效应增强。为解决这个困扰,郭寅龙课题组[101]采用稳定同位素标记(SIL)羧基结合 ESI-IMS-MS 快速分析脂肪酸,示于图 3。结果表明,d_0/d_6-DMPP 在信号增强方面具有明显的优势,其标记的脂肪酸具有相似的漂移时间、6 u 的质量偏差、特定报告离子、相似的 MS 响应,而且遵守漂移时间规则,即碳链长度和不饱和度对相对漂移时间的影响。在无色谱分离的情况下,该方法可用于正常甲状腺组织和癌组织间微量游离脂肪酸的快速检测。



注:* 代表标记为脂肪酸的 d_6-DMPP

图 3　等摩尔浓度下,d_0-DMPP 和 d_6-DMPP 标记的混合标准品 IM-MS 和 MS 图[101]

Fig. 3　IM-MS and MS spectra for a mixed test sample of d_0-DMPP and d_6-DMPP labeled standards in equal molar concentration[101]

脂肪酸与甘油三酯和磷脂相结合时,脂质分析更加复杂。Facundo 等[52]使用纳米摩擦发电结合时间对齐平行裂解(TAP)离子淌度-质谱对脂质结构进行表征。纳米摩擦发电电离时,气相的脂质发生环氧化,通过 TAP IM-MS 进行三级质谱碎裂,获得脂质的—C ═ C—位置、脂肪酰基 Sn 链的位置和组成、顺/反异构的详细信息。Meier 等[102]采用 Nano-LC-TIMS-MS/MS 分析人血浆、干细胞和癌细胞中的脂质,收集了 1 856 个脂质的 CCS 值,使已鉴定的脂质数量比标准 TIMS-MS/MS 增加了 3 倍以上。对于植物中的脂类,郭寅龙课题组[103]建立了 LC-IM-Q-TOF MS 快速定性分析烟叶中蔗糖酯的方法。正离子模式下,蔗糖酯分子形成$[M+Na]^+$,经漂移管分离、四极杆-飞行时间串联质谱仪检测,从烟叶中检出 6 类蔗糖四酯,它们在色谱柱上的保留时间相差 0.2～0.8 min,在漂移管中的漂移时间相差 0.4～0.5 ms,离子质荷比相差14 u。利用二级质谱解析,根据准分子离子的元素组成、碰撞截面积测定等对烟叶中的 6 类蔗糖四酯进行定性分析。结果表明,LC-IM-Q TOF MS 技术可以快速检测复杂样品中的蔗糖酯,结合多维数据能够显著提高定性分析的准确性。

虽然 IM-MS 在脂质分析上显示出巨大的应用潜力,但常规的分析软件一般无法直接处理仪器采集的数据,导致 IM-MS 的实际应用价值受到现有脂质结构鉴定方法的限制。近 5 年使用较多的代谢物 CCS 值数据库列于表 4。2016 年,朱正江课题组[104]首次发展机器学习算法计算代谢物的 CCS 值,并开发出可广泛用于代谢物预测的 CCS 值数据库(MetCCS)。为了解异常的甾醇脂质代谢及其在脑疾病中的作用,该课题组[105]将 IM-MS 与机器学习功能相结合,采用四维技术描绘小鼠大脑 10 个功能区域中甾醇脂质的空间分布,揭示固醇脂质数量改变、浓度变化和年龄依赖性协同调节网络的变化,并建立高覆盖率库(>2 000甾醇脂质)以准确识别甾醇脂质。此外,针对脂质类代谢物的结构特点,该课题组[106-107]发展了脂质的预测 CCS 值数据库 LipidCCS 和鉴定 CCS 值的软件 Lipid-IM MS,以准确识别非靶向的脂质代谢物,涵盖了 26 万种脂质及相应的四维结构信息(即质荷比、保留时间、碰撞截面积和二级质谱图),支持多维信息进行脂质鉴定,提高了鉴定的覆盖率和可信度。在此基础上,朱正江课题组[108]开发了第二代 CCS 值的计算方法 AllCCS,其中包含5 000多个实验测量 CCS 值和1 100多万个预测CCS值,且预测精度在2%以内,大幅

表 4 近 5 年代谢物数据库简介

Table 4 Introduction of metabolite database in recent 5 years

编号 No.	数据库 Database	年份 Year	离子淌度-质谱 IM-MS	$CCS_{实测}$ 数量 Quantity of $CCS_{measure}$	$CCS_{预测}$ 数量 Quantity of $CCS_{calculate}$	参考文献 Reference
1	MetCCS	2017	$^{DT}CCS_{N2}$	779	35203	[109]
2	LipidCCS	2017	$^{DT}CCS_{N2}$	458	63434	[110]
3	AIICCS	2020	$^{DT}CCS_{N2}$	5119	11697711	[107]
4	ISiCLE	2019	$^{DT}CCS_{N2}$	1455	> 100000	[111]
5	DeepCCS	2019	$^{DT}CCS_{N2}$, $^{TW}CCS_{N2}$	—	> 2400	[112]
6	Baker. Group	2017	$^{DT}CCS_{N2}$	> 500	—	[113]
7	Mclean. Group	2019	$^{DT}CCS_{N2}$	3800	—	[114]

* 注：$^{DT}CCS_{N2}$ 和 $^{TW}CCS_{N2}$ 代表 DTIMS 和 TWIMS 基于氮气氛围的 CCS 值测量

提升了生物体内已知和未知代谢物化学结构鉴定的准确性。

2.4 类固醇

类固醇激素参与生殖、应激和免疫反应等生命过程，是机体健康状态的关键指标[115]。类固醇激素分为皮质类固醇（糖皮质激素和盐皮质激素）、雄激素、孕激素和雌激素等 4 大类，它们来自一种常见的前体胆固醇[116]。类固醇代谢的 2 个初步阶段分别是官能化反应和共轭反应，产生的代谢物可能与原始分子具有不同的活性和毒性。采用色谱-质谱技术分析时，需要相应的标准品定性。因CCS可作为分析物识别的额外度量，IM-MS 技术在类固醇分析中得到广泛应用。为便于筛查不同样本中的类固醇，建立了类固醇的 CCS 值数据库[58,117-118]。

郭寅龙课题组[119]将吡啶和亚硫酰氯作为衍生试剂，通过一步衍生化反应，脂肪醇、脂肪醛和甾醇的检测灵敏度得到显著提高，并结合 ESI-IM-MS 快速分析甲状腺癌组织和癌旁正常组织中的 15 种脂肪醇、脂肪醛和甾醇，示于图 4。结果表明，2 种组织中某些分析物的含量存在显著差异（$p<0.05$），甲状腺癌组织中大多数分析物之间的相关性优于癌旁正常组织中的相关性。

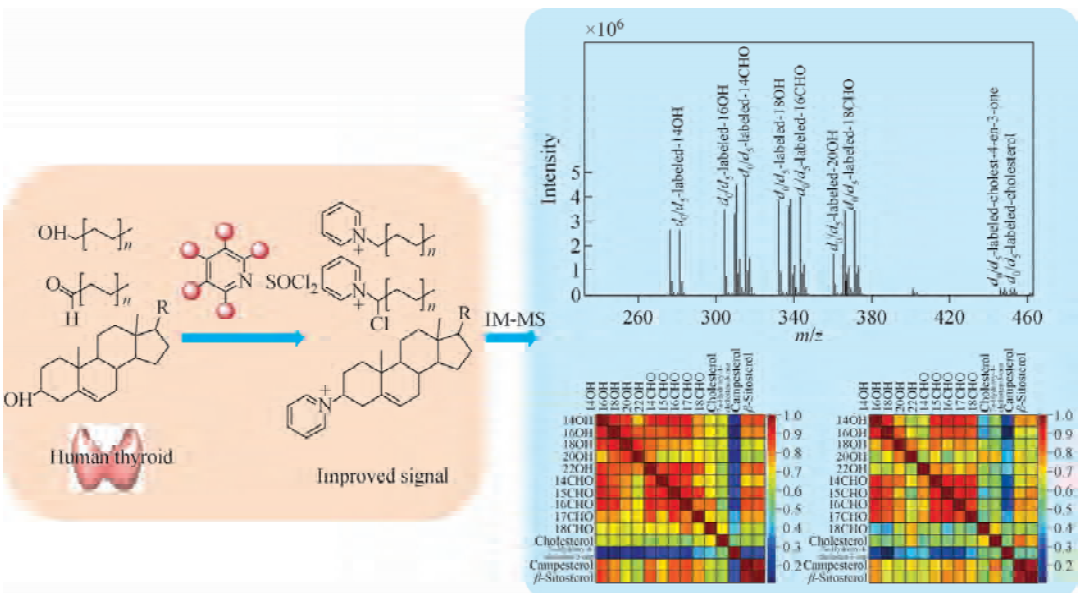


图 4 基于衍生化的电喷雾-离子淌度-质谱法同时分析甲状腺组织中的脂肪醇、脂肪醛和甾醇[119]

Fig. 4 Simultaneous analysis of fatty alcohols, fatty aldehydes, and sterols in thyroid tissues by electrospray ionization-ion mobility-mass spectrometry based on charge derivatization[119]

蛋白同化类固醇代谢物的检测和鉴定在临床、法医学和兴奋剂分析中至关重要。Chouinard 等[120-121]以睾酮和表睾酮为例,分别使用臭氧诱导环内碳碳双键裂解和 Paternò-Büchi 反应衍生化内源性类固醇。结果表明,经臭氧的裂解,睾酮和表睾酮产生独特、稳定的气相构象及碰撞截面;在低压汞灯下,睾酮和表睾酮经 Paternò-Büchi 反应形成甾体氧烷,可产生独特的离子迁移谱,使每种异构体具备独特的指纹,这 2 种方法均可提高违禁物识别的准确性。Colin 等[122]建立了 LC-FAIMS-MS 法分析尿中 7 种合成代谢雄激素类固醇的葡萄糖醛酸和硫酸盐代谢产物,根据不同模式下每种代谢物所特有的醋酸钠簇鉴定类固醇代谢物,正离子模式下,对阳离子加合物(H^+、NH_4^+、Na^+、K^+和 Cs^+)进行分离,发现减少基质干扰,无标记尿液中二钠固醇代谢物加合物的信噪比会增加(>250%)。McLean 等[123]开发了 LC-IM-HRMS 方法进行完整Ⅱ期类固醇代谢物的多维分离以增加峰值容量,利用 IM 的碰撞截面积值作为另一维度的分子表征方法以提高选择性,并改进了低浓度下完整类固醇分析的识别。

2.5　聚糖

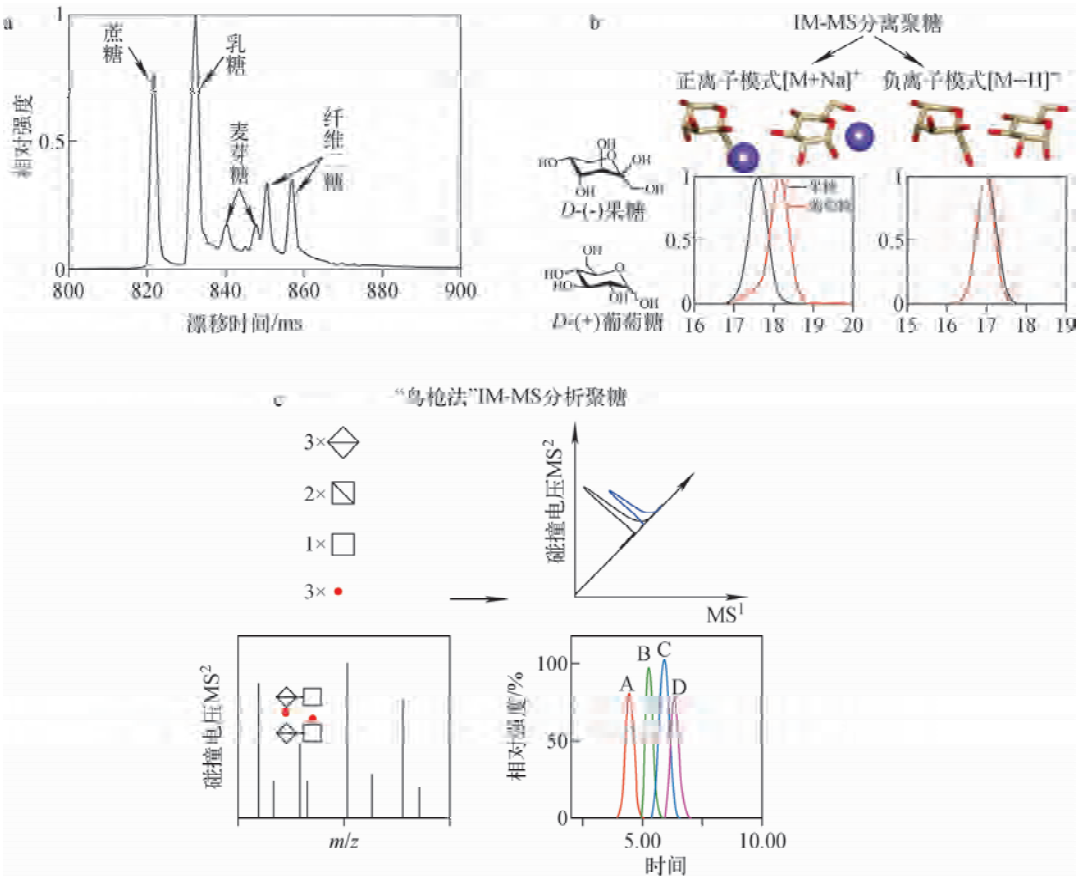
聚糖影响糖蛋白在细胞内的靶向运输,参与糖蛋白新生肽链的折叠或聚合和分子间的识别。然而,聚糖包含了多种结构上细微差异的连接异构体、位置异构体和组成异构体,常见的有 *N*-连接聚糖[124-127]和 *O*-连接聚糖[128-129]。由于缺乏能够表征糖苷键和单糖的分析工具,导致分析聚糖的结构和功能受阻,相比多肽、寡核苷酸,表征聚糖的难度更大[130-131]。聚糖是亲水性分子,需衍生化后再进行反相色谱分离。质谱法仅需少量样品,且易与色谱耦合,可使用不同的裂解策略产生结构信息,是分析聚糖的首选方法。然而,由于单糖异构体和糖苷键的多样性,仅通过碎片信息不足以完整描述聚糖结构。因此,需要分离聚糖,并结合裂解数据和生物合成途径预测聚糖结构。最初,IM 在聚糖分析中的应用集中在小分子聚糖异构体的标准品,随着仪器水平提升和商业化程度增加,IM-MS 联用技术被用于分离多种样本来源的聚糖异构体[132]。

目前,聚糖检测主要分为完整聚糖的直接分析和利用质谱碎裂功能进行碎片分析 2 种策略[133],示于图 5。由于聚糖能形成离子淌度强度、迁移率差异大的正离子或负离子[134],分析完整聚糖时可进行直接分析或在样品中添加金属阳离子形成复合物。IM-MS 也可实现对聚糖分子的直接分析,但对仪器分辨率要求较高。有报道[135]利用 SLIM 的蛇形超长路径结构 SLIM SUPER IM-MS 实现了完整聚糖高分辨分析,该平台为糖化学提供了极具潜力的思路。在样品中添加金属阳离子可促进非共价复合物的形成,通常二价金属加合物的分离效果最好。Baker 等[136]比较了二价金属 Mn^{2+}、Cu^{2+}和 Zn^{2+}强化聚糖异构体在正、负离子模式下的 IMS-MS 分离效果,采用 IMS-Q TOF MS 表征糖苷键(α 或 β)的不同构型、不同线性或分支连接性引起的细微结构差异的聚糖标准品。结果表明,正、负离子模式切换时,聚糖的 IMS 图改变,添加金属离子可导致聚糖构象发生显著变化,并通过金属络合实现异构体基线分离。随着分子尺寸的增大,检测分子中细微结构差异越来越困难,可采用"鸟枪式"IM-MS 测序分析裂解的碎片离子,以确定聚糖生物活性序列的确切信息。Pagel 等[137]在离子淌度-质谱仪中解离完整的硫酸乙酰肝素,并测量碎片的碰撞截面值,将完整离子和碎片离子的数据与 36 个已知结构的硫酸乙酰肝素糖结构(从二糖到十糖)进行匹配,以确定验证标准和未知天然糖的序列。

2.6　其他代谢产物

除常见的小分子代谢物外,植物的次生代谢产物研究也受到关注。郭寅龙课题组[138]采用高分辨 U 形离子淌度分析器分析了广陈皮中多甲氧基黄酮,结果表明,ESI-UMA-MS 可使橘皮素和甜橙黄酮达到完全分离。而在相同条件下,采用 DTIMS-MS 仅表现出分离的趋势[139]。这表明 ESI-UMA-MS 在天然产物分析中有着广阔的应用前景[140]。

生物液体中的胍基化合物(GCs)和脲基化合物(UCs)浓度较低,但在生物活动中发挥着重要作用[141],同时检测这 2 类化合物具有重要的临床价值。郭寅龙课题组[142]采用苄基重排稳定同位素标记(BRSIL)结合 LC-DTIMS-MS 高通量地筛选和定量人甲状腺组织中的GCs



注：a. 直接分析聚糖分子；b. 非共价复合物；c. 质谱碎裂分析

图 5 IM-MS 分析聚糖的 2 种策略

Fig. 5 Two strategies for analyzing glycans by IM-MS

和 UCs。结果表明，短的反相色谱柱可实现在线脱盐和 5 min 的分析周期，根据三维离子特征（保留时间、漂移时间、质荷比）得出的离子丰度可用于定量甲状腺组织中的 GCs 和 UCs。BRSIL 与 LC-DTIMS-Q TOF MS 联用可作为研究人类甲状腺组织中 GCs 和 UCs 的有力工具。

3 总结与展望

小分子代谢物存在于生物体的各种代谢过程，涵盖大量的化合物类别。由于样本量较少、目标化合物丰度低、普遍存在同分异构体，单独采用质谱法不足以对代谢物进行准确分析。IM-MS 技术可以大幅提升对小分子代谢物分析的灵敏度和准确性，极大降低各种复杂体系中同分异构体的分离和分析难度。随着仪器技术的快速发展，高分辨离子淌度-质谱不仅可简化同分异构体的分离工作，而且可通过 CCS 值提高化合物鉴定的可信度。未来潜在的发展趋势主要有以下 2 方面：1）识别机体产生的代谢物有助于理解生理和病理的变化、发现疾病标志物。小分子代谢物包含大量已知和未知的代谢物，准确鉴定小分子代谢物存在缺乏高覆盖率的标准谱图、缺少用于结构解析的特征碎片及易受实验条件影响等难点。幸运的是，IM-MS 技术可提供多维信息表征代谢物，通过建立相关 CCS 数据库能够对代谢物进行可靠的注解，从而全面了解、揭示代谢物在生物过程中的作用。2）基于 IM-MS 技术的先进分析方法为天然产物的药物发现提供了工具，其强大的分离能力可以提升天然产物的分析、表征准确性。未来，IM-MS 技术在药物发现和天然产物分析等领域的应用将会迅速增长，具有广阔的应用前景。

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