Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Biology

The application of ion mobility mass spectrometry to metabolomics

Xing Zhang, Kevin Quinn, Charmion Cruickshank-Quinn, Richard Reisdorph and Nichole Reisdorph

Mass spectrometry-based metabolomics is being increasingly utilized in various research fields including investigating human diseases, nutrition, industrial applications, and plant/natural products studies. Although new analytical approaches have enhanced the performance of metabolomic analyses, significant challenges associated with throughput, metabolome coverage, and compound identification still exist. Ion mobility mass spectrometry offers great potential for improving throughput and depth of coverage in metabolomics experiments. For example, multi-dimensional, structural resolution offered by ion mobility enables improved identification of metabolites and chemical classes. This mini-review discusses the advantages, recent developments and limitations of using ion mobility mass spectrometry as part of a metabolomics workflow.

Address
Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, United States

Corresponding author: Reisdorph, Nichole (nichole.reisdorph@ucdenver.edu)

Current Opinion in Chemical Biology 2018, **42**:60–66

This review comes from a themed issue on **Omics**

Edited by **Erin Baker** and **Perdita Barran**

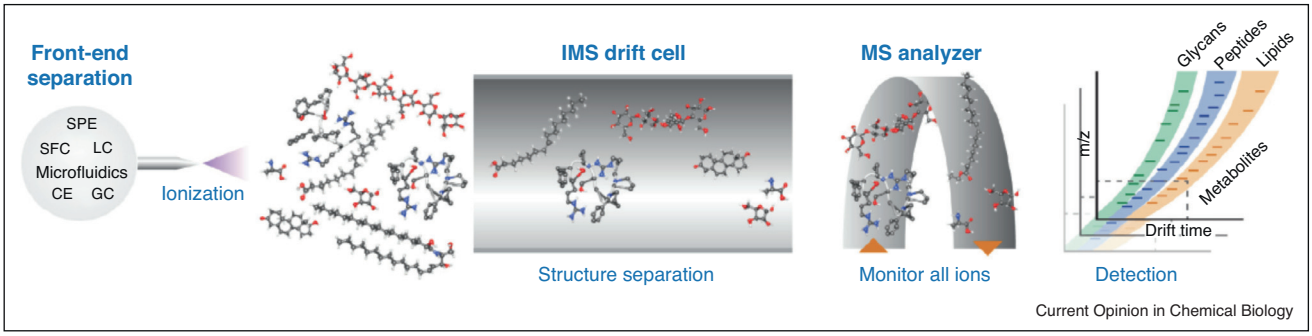
http://dx.doi.org/10.1016/j.cbpa.2017.11.001

Introduction

Metabolomics [1–3] has become a well-accepted approach for the comprehensive analysis of a wide range of low-molecular weight (<1500 Da) compounds; applications include understanding molecular mechanisms [3], nutrition [4], and human health and disease [5–7]. In mass spectrometry-based metabolomics [8,9], two general strategies are used for these purposes: targeted and untargeted metabolomics. Targeted metabolomics [10–12] is an indispensable part of a metabolomics workflow because it can provide a means for the absolute quantitation of known and candidate biomarkers, thereby providing validation. However, targeted approaches quantitate a relatively small number of metabolites at a time; therefore, overall coverage of the metabolome is limited. In contrast, untargeted metabolomics [13–15] measures up to thousands of molecular features at a time; these span a wide range of molecular classes. Therefore, untargeted metabolomics is useful for providing a large amount of information when hypothesis generation and biomarker discovery are the goals. However, there are several technical challenges in mass spectrometry-based untargeted metabolomics, including the following: (1) wide variations in chemical and physical properties of small molecules limit metabolome coverage due to differences in extraction techniques [16,17]; (2) the use of front end chromatography to resolve thousands of molecules within a metabolome makes high throughput analyses challenging [18–22]; (3) metabolite identification is confounded by numerous factors, including the existence of compounds with identical masses such as isomers and isobars [23–26]. An analytical platform that can provide high throughput analysis with confident identification of a wide range of metabolite classes could be considered the next evolution in untargeted metabolomics.

In spite of challenges, MS-based metabolomics offers high sensitivity, wide chemical class coverage, and straightforward spectrum interpretation. The integration [27,28•,29,30] of ion mobility spectrometry (IMS) with MS has emerged as an improved approach for small molecule analysis over the past 2–3 decades, offering both structural and mass information for detected ions within milliseconds. IMS [31] is a gas-phase electrophoretic technique that enables rapid separation of ions based on their size, shape, and charge state. This is achieved by ion-neutral collisions in a buffer gas when ions travel through a drift cell under a defined electric field. When using IMS, collisional cross section (CCS) values, representing the rotationally averaged apparent surface area of the ions, can be generated [32•,33,34••,35]. The CCS value is a unique physicochemical property of a molecule, and can aid in compound identification [36,37]. This comes with caveats, including the fact that CCS values cannot be calculated when polar modifiers/additives are used to enhance separation in the mobility cell [34••]. Being orthogonal to MS separation, ion mobility also provides mobility-mass correlations [38,39•,40] and improves the signal-to-noise ratio [29,41] when the technologies are integrated into an ion mobility mass spectrometry (IMMS) platform. The additional resolution offered by an IMMS platform makes the high throughput

Figure 1



Schematic of IMMS analysis workflow with different types of front-end separation techniques. Reproduced from Ref. [53]. Copyright 2017 Annual Reviews. *Abbreviations*: SPE, solid phase extraction; SFC, supercritical fluidic chromatography; LC, liquid chromatography; CE, capillary electrophoresis; GC, gas chromatography.

resolution of thousands of compounds more feasible compared to an MS-only platform. Overall, potential improvements in metabolite identification and resolution make IMMS an appealing approach for metabolomics analysis.

Instruments and methods

Although IMMS has been in use for decades, its application to metabolomics is more recent, in part due to the availability of commercial systems. Currently, four major types of IMMS technologies are commercially available, including drift time IMMS (DTIMMS) [28•,42], traveling wave IMMS (TWIMMS) [43,44••], differential mobility MS (DMS) [45], and trapped IMMS (TIMMS) [46]. Although time-of-flight (TOF) is the predominant mass analyzer coupled to IMS, IMS has also been coupled with triple quadrupole, ion trap and Orbitrap mass spectrometers [27,47]. IMMS is adaptable to various types of ionization sources such as electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) and matrix assisted laser desorption ionization (MALDI), making it suitable for analyzing a wide range of analytes. Other upfront techniques, including gas chromatography, capillary electrophoresis and supercritical fluid chromatography, can also be integrated into an IMMS system; while the application of these strategies is currently limited, they may prove promising in the future.

Among many types of ion mobility spectrometers, DTIMS and TWIMS have been most extensively utilized for metabolomics analysis in the past decade. As noted above, other configurations include differential mobility and TIMMS, which are not as commonly used but also have potential utility in metabolomics [48–51]. Early studies mostly employed direct flow injection analysis (FIA) or MALDI with IMMS analysis. For example, Kaplan *et al.* investigated lymph fluid metabolomes from fasting and fed rats by a home-built ESI-IM-QTOFMS [52]. Williams *et al.* characterized metabolic changes in human colorectal cancer tissues using Synapt G2-S TWIMMS [53] (Waters Corporation, Manchester, UK). Jackson *et al.* profiled the phospholipids in rat brain tissue with MALDI-IM-TOFMS [54] (Ionwerk Inc., Houston, USA). Some manufacturer's offer high field asymmetric ion mobility spectrometry (FAIMS), an ambient pressure IMS technique, as a custom modification over integral IMS [55]. Although IMMS has proven to be an effective analytical approach for metabolomics analysis, FIA is not an ideal way to deliver complex samples for IMMS because competition during ionization among different ion species results in ionization suppression. Therefore, utilizing FIA for sample introduction into IMMS largely limits metabolome coverage when performing untargeted metabolomics analysis.

In recent years, various front-end separation techniques have been successfully coupled with IMMS to improve the performance of complex mixture analysis [56•,57•]. Figure 1 [57•] shows the schematic of coupling different front-end separation techniques prior to the IMS separation and MS detection. By separating the components using strategies such as liquid chromatography (LC) and gas chromatography (GC), ionization suppression can be largely reduced. Coupling LC with IMMS is appealing within the field of metabolomics because IMS facilitates the separation and identification of molecules while the coverage of the metabolome is maintained. For example, Harry *et al.* developed a LC–IMMS platform for urine metabolomics by coupling reverse-phase LC with DTIMMS to enhance the coverage and spectral quality [58]. A review [44••] by Paglia *et al.* describes how LC–IMMS has been used to support metabolomics and lipidomics research and includes a detailed workflow. Although utilizing a traditional LC method for front-end separation for IMMS metabolomics analysis improves metabolite resolution and therefore metabolome coverage, the minute-long to hour-long gradient time remains a limiting factor for large-scale metabolomics analysis.

Zhang *et al.* first proposed a low-resolution LC chromatographic separation prior to IMMS analysis to