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Small molecule MALDI MS imaging: Current technologies and future challenges

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A B S T R A C T

Imaging of specific small molecules is particularly challenging using conventional optical microscopy techniques. This has led to the development of alternative imaging modalities, including mass spectrometry (MS)-based methods. This review aims to provide an overview of the technologies, methods and future directions of laser-based mass spectrometry imaging (MSI) of small molecules. In particular it will focus on matrix-assisted laser desorption/ionization (MALDI) as the ion source, although other laser mass spectrometry methods will also be discussed to provide context, both historical and current.

Small molecule MALDI MSI has been performed on a wide variety of instrument platforms: these are reviewed, as are the laser systems that are commonly used in this technique.

Instrumentation and methodology cross over in the areas of achieving optimal spatial resolution, a key parameter in obtaining meaningful data. Also discussed is sample preparation, which is pivotal in maintaining sample integrity, providing a true reflection of the distribution of analytes, spatial resolution and sensitivity.

Like all developing analytical techniques there are challenges to be overcome. Two of these are dealing with sample complexity and obtaining quantitative information from an imaging experiment. Both of these topics are addressed.

Finally, novel experiments including non-MALDI laser ionization techniques are highlighted and a future perspective on the role of MALDI MSI in the small molecule arena is provided.

Contents

Abbreviations: MSI, Mass Spectrometry Imaging; IMS, Ion Mobility Separation; LDI, Laser Desorption/Ionization; MALDI, Matrix-Assisted Laser Desorption/Ionization; SIMS, Secondary Ion Mass Spectrometry; DESI, Desorption Electrospray Ionization; TOF, Time-Of-Flight; LAMMA, Laser Microprobe Mass Analyzer; Nd:YAG, Neodymium-Doped Yttrium Aluminum Garnet; Q-TOF, Quadrupole-TOF; QIT-TOF, Quadrupole Ion Trap TOF; FT-ICR, Fourier Transform Ion Cyclotron Resonance; APCI, Atmospheric Pressure Chemical Ionization; ICP, Inductively Coupled Plasma; ESI, Electrospray Ionization; FWHM, Full Width at Half Maximum; Nd:YVO_4, Neodymium-Doped Yttrium Ortho Vanadate; Nd:YLF, Neodymium-doped Yttrium Lithium Fluoride; LA, Laser Ablation; MALDESI, Matrix-Assisted Laser Desorption Electrospray Ionization.

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1. Introduction

This review is focused on small molecule imaging using laser-based mass spectrometry (MS), in particular matrix-assisted laser desorption/ionization (MALDI). It will examine the role of instrumentation, methods, current challenges and a future perspective. To provide context, the rich history of laser-based mass spectrometry imaging (MSI) will also be discussed. Large molecule imaging or specific applications of MSI will not be covered as both have been extensively covered by previous reviews [1–4]. As will become apparent, small molecule imaging was the original form of laser-based MSI. It also has been an area that has seen much greater variety in terms of mass spectrometers, laser wavelengths and ionization methods used. This is largely due to the fact that mass spectrometers are at their most efficient when analyzing small molecules [5,6]. Small molecule MSI, the focus of this review, belongs to the wider field of MALDI MSI. MALDI MSI is an area of intense and growing research interest with more than 1500 peer reviewed publications on MALDI MSI at the time of writing (source PubMed, search term "MALDI imaging"). Where appropriate, the reader is referred to detailed reviews on specific aspects of this technique which are beyond the scope of this review.

2. What is MSI?

MSI is a form of surface analysis, where ions are generated from a surface and detected using a mass spectrometer. In laser-based MSI, the surface of interest is irradiated with a laser. The laser energy desorbs atoms and molecules from the sample surface. Some of the desorbed species are ionized, either by the ablating laser or through a secondary process, *e.g.* post desorption laser ionization with a second laser. These ions are then mass analyzed to determine the chemical composition of the sample and to gain an appreciation of the amount of the molecular species present. The latter quantitative aspect of the experiment is challenging and will be discussed in greater detail later. Many different surfaces can be studied, *e.g.* polymers, semiconductors, plant or animal tissues [7–10].

What sets MSI apart from other laser desorption/ionization MS experiments is that spatial coordinates are assigned to the mass spectra generated, *i.e.* x- and y-coordinates. This spatial information can then be used to make an ion map of the surface under investigation, typically using a color scale to indicate ion intensity.

Two methods are employed to ensure data are recorded from a specific location. The most commonly used is a scanning technique, analogous to scanning electron microscopy. A small sample area is irradiated by the laser and coordinates and a mass spectrum are recorded for this locus. The sample is moved and the process is repeated many times to cover the desired area to be analyzed (microprobe analysis) [11].

In the other, 'microscope', approach a larger area is irradiated with the laser and a space-sensitive detector is utilized to provide the spatial information [12,13]. This approach is theoretically capable of much higher spatial resolution than scanning techniques,

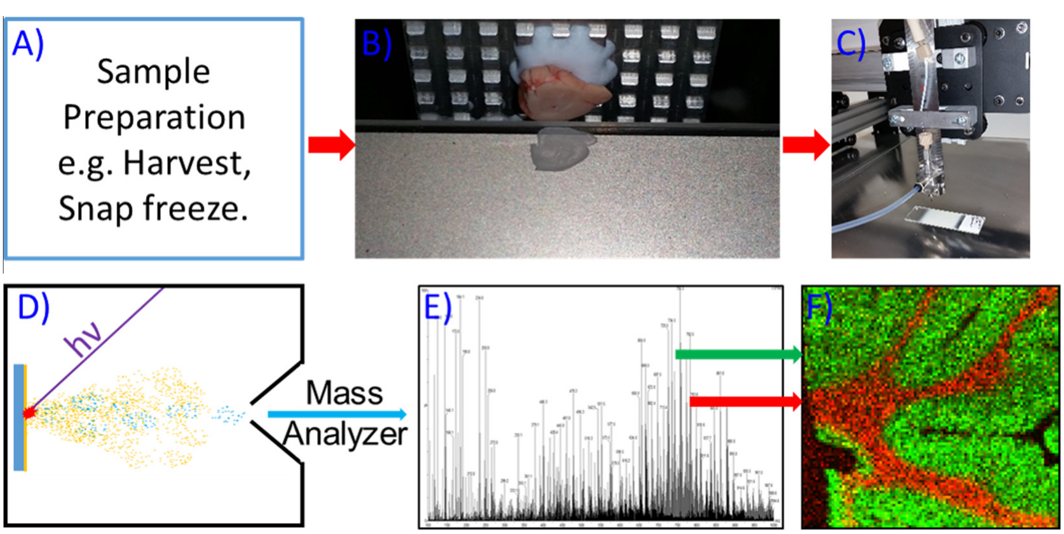

Fig. 1. Typical MALDI MSI workflow for tissue analysis. (A) Sample preparation including tissue harvesting and snap freezing. (B) Thin sections are cut using a cryotome. (C) MALDI matrix is applied. (D) Data acquisition using a mass spectrometer with a MALDI source. (E) Mass spectrum generated for each position. (F) Image generation and analysis.

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