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Imaging and spatially resolved quantification of drug distribution in tissues by mass spectrometry

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Mass spectrometry imaging (MSI) is a powerful label-free technique for visualizing drug and metabolite distributions in biological tissues. In this review, we discuss recent developments in MSI and spatial profiling technologies to visualize and quantify drug distributions in tissues. We also present recent examples of applications of these technologies for assessing drug distribution within tissues and individual cells. Finally, we focus on an emerging technique coupling laser capture microdissection (LCM) to quantitative mass spectrometry, which combines the respective advantages of imaging and conventional liquid chromatography mass spectrometry, and thus enables spatially resolved drug quantification.

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Introduction

To exert its desired activity, a drug must reach the biological target at its exact location (host cell or pathogen) at sufficient concentration. Drug and metabolite concentrations measured in plasma often provide poor representation of drug exposure at target tissues or cells, and are not always sufficient for accurate interpretation and understanding of efficacy within the body.

Mass spectrometry imaging (MSI) is a powerful label-free technique for the *in situ* analysis of drug and metabolite distributions within *ex vivo* tissues. MSI produces valuable spatial and molecule-specific information, complementary to that acquired by traditional analytical approaches, such as quantitative autoradiography (QWBA) and liquid chromatography mass spectrometry (LC/MS/MS) of tissue homogenates [1–4,5•]. Significant spatial information is lost during tissue homogenization before quantification of drugs by LC/MS/MS. Autoradiography offers high spatial detail, but lacks molecular specificity as only the label of administered radiolabeled drug is detected [6]. As MSI techniques detect drug and metabolite molecules directly, they offer the unique opportunity to spatially resolve metabolites from their parent drugs.

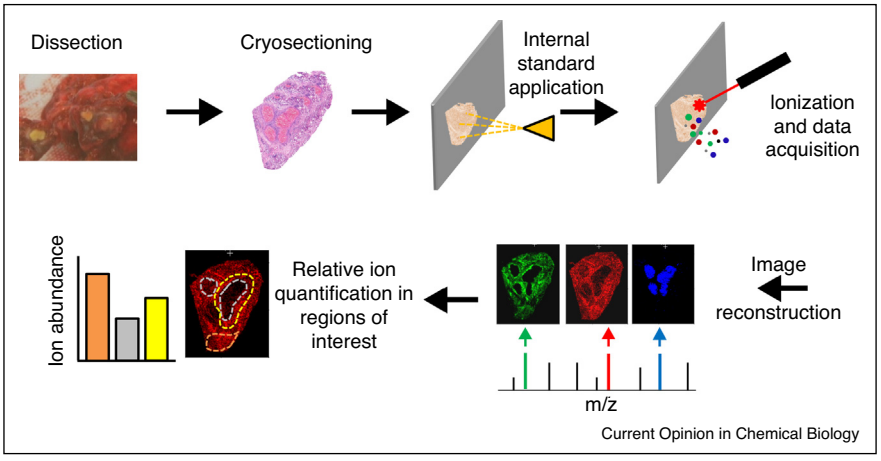
In a standard MSI experiment, an ionization beam (typically a laser, solvent stream, or primary ion source) is rastered across the tissue surface, and mass spectra are acquired at defined (x,y) coordinates. A two-dimensional (2D) ion distribution map is reconstructed using software, in which a mass spectrum is generated for each pixel. Correlating drug MS images with histologically stained adjacent tissue sections allows for accurate interpretation of drug delivery to specific tissues, cells and/or pathogens. A schematic representation of a typical MSI workflow applied to drug imaging in tissue is shown in Figure 1. MSI of drugs and other small molecules in tissues has been previously reviewed in depth [7–9]. The aim of this review is to discuss recent technological advances in the field, with particular focus on spatial resolution and quantification capabilities. A summary of the MS imaging and spatial profiling methods discussed in this paper including required sample preparation protocols is presented in Table 1.

Mass spectrometry imaging technologies

Matrix-assisted laser desorption ionization MS (MALDI-MS) remains the most widely applied ionization method for tissue imaging due to its sensitivity, large dynamic range of masses covered, and the relatively high availability of commercial MALDI mass spectrometers. Recent improvements in laser optics have enabled imaging of drug distribution in tissues at sub 10 μm lateral resolutions [10,11••], opening new avenues for subcellular drug localization. However, the increase in lateral resolution reduces sampling volume and ion yield, resulting in reduced analytical sensitivity.

The sensitivity in MALDI-MS imaging is often limited by ionization efficiency. *In situ* chemical derivatization of selected drugs has been shown to dramatically increase

Figure 1



Representative schematic of mass spectrometry imaging (MSI) workflow for drug imaging in biological tissue sections (adapted with permission from [4]. *m/z*: mass to charge ratio.

Table 1

Table summarizing common MS imaging and profiling techniques used for drug localization in tissues and cells. The speed of sample preparation, speed of MS image acquisition, and analytical sensitivity are rated from 1 to 5 (in order of increasing speed or sensitivity). Speed of MS image acquisition depends upon the pixel and overall tissue dimensions as well as MS scan/dwell time. Analytical sensitivity is heavily dependent upon ionization properties, which are highly drug specific. The sensitivity rating is therefore only meant as a guide and should be carefully evaluated for each drug analyzed

	MALDI-MSI	Laser ablation/ desorption-MSI	SIMS-MSI	DESI-MSI	Nano-DESI-MSI	LMJ-SS	LCM-ESI or LCM-LC/MS
Tissue preparation	Thin cryo-sections (5–50 μm)	Thin cryo-sections (10–50 μm)	Cultured cells or bacteria	Thin cryo-sections (5–50 μm), intact tissues	Thin cryo-sections (5–20 μm)	Thin cryo-sections (10–50 μm)	Thin cryo-sections (10–30 μm)
Requires matrix?	Yes	No	No	No	No	No	No
Ionization pressure	Vacuum or atmospheric	Vacuum or atmospheric	Vacuum	Atmospheric	Atmospheric	Atmospheric	Atmospheric
Speed of sample preparation	**	*****	*****	*****	*****	*****	**
Speed of MS acquisition	***	***	**	****	**	*****	**** (ESI) ** (LC/MS)
Sensitivity	***	**	*	**	**	****	*****
Lateral resolution	<10 μm	>100 μm	<250 nm	>200 μm	>10 μm	>500 μm	>20 μm
Imaging mode	Imaging	Imaging	Imaging	Imaging/profiling	Imaging	Profiling/imaging	Profiling
References	[1–4,5•,10, 11••,12,13, 26,27,29,43, 45,46,49]	[14,25]	[16••, 17••,18•]	[20•,21]	[22–24]	[28–32]	[33,34,25,36]

the ion yield [12,13], opening previously unsuitable classes of drugs to MSI. The addition of a laser-induced postionization step following initial MALDI ionization can enhance the analytical sensitivity for many small molecules by up to two orders of magnitude, even when sampling from pixels as small as 5 μm wide [11••]. A similar postionization method has been applied at lower lateral resolution in a quantitative matrix-free approach to image drug distributions in a mouse model [14]. In this study, the antibiotic drug acriflavine was imaged in *ex vivo* kidney tissue at a spatial resolution of 500 μm with a calculated limit of quantification (LOQ) of 500 nmol per mm^2 of tissue area.

Of all MSI ionization methods, secondary ion mass spectrometry (SIMS) offers the highest spatial resolving