

Advantages and limitations of Quantitative Mass Spectrometry Imaging in pharmaco-toxicology area

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Introduction: Mass Spectrometry Imaging (MSI) is able to simultaneously record the distribution of hundreds of biomolecules or drugs directly from tissue, without labeling and without prior knowledge (1). MSI based on matrix assisted laser desorption/ionization (MALDI) applied with different tissue preparation procedures can be used to analyze proteins, peptides, glycans, lipids, metabolites and drug (1,2). With a multimodal platform combining quantitative mass spectrometry imaging (QMSI), histochemistry, immunohistochemistry and data science, it is possible to evaluate the drug efficacy, its impact on biomarkers, the target exposure and potential toxicological effects.

Methods: A biological sample, like an organ (kidney, brain, liver or tumor) is sectioned with a cryostat and mounted on a conductive slide. A MALDI matrix is sprayed onto the section sample (between 8 and 20 µm thickness) with an automatic TM sprayer (HTX Technologies, LLC) prior analysis. Data acquisition is performed using 7T MALDI-FTICR (Solarix, Bruker Daltonics) at a determined (between 20 and 300 µm) spatial resolution in full scan mode (positive or negative mode, depending the ionization of the compound of interest). Acquired data are treated with Multimaging™ (ImaBiotech). Histological and immunohistochemical staining could also be applied. Quantitative results of drugs and metabolites of interest could be confirmed by LC-MS/MS. Sometimes, an additional step (derivatization strategy) to increase the sensitivity is necessary.

Results: Using the mass spectrometry imaging platform, quantification is possible for endogenous metabolites and drugs, while keeping the histological localization. The drug localization and quantification in sample confirm or not the target exposure. With this technique, toxicological effects can be determined, by visualizing the drug in a particular structure of the organ. Correlation between molecular imaging and staining can help to cross-link histological lesions and molecular up and down regulated expressions. Furthermore, this kind of work allows monitoring proximal pharmacodynamics biomarkers of drug efficacy and response to treatment, by measuring the early metabolic response (for example: tryptophan and kynurenine endogenous levels, inflammatory responses (lipids modulation), arginine and ornithine levels, oxidative stress). Furthermore, we can show the correlation between drug presence and target modulation in the microenvironment, and by screening metabolites that are involved in other pathways (like TCA cycle or energetic pathway).

Conclusion: QMSI allows studying the pharmacological effect of the drug directly in tissue, showing its histological localization and its impact on the endogenous biomarkers. QMSI has the advantages of allowing following the label free biodistribution of a compound of interest (about 2000 molecules at the same time), with a molecular specificity, while preserving the histological integrity, while being quantitative. However, some molecules lack sensitivity with this technique, a problem that could be circumvented by derivatization reactions, matrix optimization, or tissue washing.

References

1. Seeley EH, Caprioli RM. Chapter 25 - Imaging Mass Spectrometry of Intact Biomolecules in Tissue Sections. In: Issaq HJ, Veenstra TD, editors. Proteomic and Metabolomic Approaches to Biomarker Discovery [Internet]. Boston: Academic Press; 2013. p. 393–406.
2. Hochart G, Hamm G, Stauber J. Label-free MS imaging from drug discovery to preclinical development. *Bioanalysis*. 2014 Oct;6(20):2775–88.

Conflict of interest : none