

# MALDI mass spectrometric imaging methods for localization and identification of pathophysiological relevant regulators in tissue samples

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# Chapter 8

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## Societal impact

Clinical research allows us the chance and the opportunity to develop and improve our lives through new knowledge. Cardiovascular disease (CVD) still remained the leading cause of death worldwide [1], also chronic kidney disease (CKD) represents an increasing health burden worldwide [2]. Furthermore, there is also increasing evidence that CKD has a strong influence on both the development and progression of CVD [3-8].

The pathology and manifestations of CVD differ in CKD compared with the population without CKD [9]. Despite the high clinical relevance of CKD-associated CVD, the underlying mechanisms have not been fully elucidated until today [9]. The decoding of these mechanisms is of enormous importance for the adaptation and development of new therapies to combat these diseases.

Mass spectrometry is a unique technique for identifying various substances by detection of the molecular weight of specific target proteins. Mass spectrometry analysis detects biological protein processing steps such as post-translational modifications [10-13]. PTMs are of great importance for the underlying mechanisms of the major common diseases CKD and CVD [12, 13]. The identification of post-translational modifications which cannot be stained nor detected with antibodies makes mass spectrometry an indispensable analytical method in basic research. The use of mass spectrometric imaging provides an in-depth, molecular understanding of the pathology of CKD-associated CVD [12-14].

Currently, mass-spectrometric methods are available in clinical research mainly in highly specialized laboratories, but currently not established in routine diagnostics. In this context, investment costs are the major barrier. However, the recent development of MS shows the potential to complement clinical laboratory methods. However, the approaches are still quite far from clinical application. The major limitations remain standardization and low throughput of measurements, user-friendliness of the equipment, and especially data analysis. Due to the high complexity of the methodology and data volumes, expert knowledge is currently still required to obtain valid and reproducible results.

**The development of novel methods and the optimization of these methods for routine clinical use is an important step and are present in this thesis.**

In the first part of this thesis, a standard operation protocol "SOP" for sample preparation of FFPE tissue samples was established [15]. In particular, the mass spectrometric methods were used to identify and localize post-translational modifications of proteins, peptides and lipoproteins in tissue samples.

In the second part of this thesis, an algorithm was developed to combine histological images and MALDI imaging data and therefore extend them to the molecular level [14]. The image data of different sources are automatically registered and a 3D model is reconstructed based on these data. The virtual model of the previously analyzed tissue is visualized in a combined 3-dimensional model. The possibility to rotate, slice the model and decide individually which images to combine provides a powerful analysis approach, rather than viewing the images of each slice in sequence. Combining these imaging modalities in a 3-dimensional will increase the information content of tissue samples in the future. This approach will enable a molecular and microscopic analysis of tissue samples in clinical research and diagnostics.

Through the development and advancement of mass spectrometry imaging, this thesis will contribute to a more detailed understanding of the biological processes and mechanisms in CVD and CKD and the development of even more specific and effective therapeutic strategies.

Through publications in scientific journals, poster presentations, and oral presentations, the results were shared with both the scientific community and the general public.

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