Maastricht University

Local metabolism in preclinical disease models studied with mass spectrometry imaging

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Chapter 6

Impact

In this thesis, MALDI mass spectrometry imaging (MSI) has been applied to study the local metabolism of atherosclerosis, abdominal fascia healing, and non-small cell lung carcinoma in several different animal models. It is important to realize not only the underlying scientific impact, but also other non-academic benefits such as societal and economic relevance, arising from this scientific research. In the following sections, I will briefly discuss aspects of the impact of the studies described in this thesis.

Scientific impact

In **chapter 2**, I systematically investigated lipids in atherosclerotic plaques formed in the two most widely used atherosclerotic mouse models using MALDI-MSI. Since the differences between these two models are poorly understood and well-standardized comparative studies are scarce, the systemic characterization of atherosclerotic lipids in these two models could have a significant impact on preclinical atherosclerosis research. Fellow researchers and research firms can benefit from this published work for selecting mouse models for their future atherosclerotic studies. Moreover, one aorta root was imaged comprehensively by 3D-MALDI-MSI to investigate the volumetric distribution of the plaque-specific lipids along the plaque's length. Expanding 2D-MSI to a three-dimensional rendered volume enables a closer representation of the native 3D biological structure and yields new insights of the molecular complexity and heterogeneity of biological systems, and thereby demonstrates its potential value for clinical 3D imaging application.

Following the same line, in **chapter 3**, I combined non-targeted MALDI-MSI metabolomics of mouse aortic tissue with targeted metabolomics of human plasma using SRM-LC-MS/MS. Combining the plasma, which represents the systemic state of the organism with the local metabolism of the disease, offers a more comprehensive, holistic strategy to understand atherosclerosis mechanisms. Moreover, this novel integration workflow not only strengthens MALDI-MSI as a discovery tool but also widely complements the mechanistic study already performed by MSI towards a novel tool for diagnosis, because clinicians routinely assess an individual's overall health status by measuring certain metabolites in biofluids. Additionally, the investigation of the individual's metabolic conditions in both tissue and plasma has a profound effect upon precision or personalized medical initiatives.

In **chapter 4**, the local lipids alterations of fascial healing revealed by MSI were correlated to histologically (H&E) scored changes captured by microscopic imaging. This correlative study required a close cooperation among surgeons, MSI researchers, and pathologists, leading to a better understanding of molecular and cellular changes during acute fascia healing, as well as novel therapeutic targets that allow prevention or treatment of incisional hernias.

In the last chapter of this thesis (**chapter 5**), using stable isotope (^{13}C) labeling and MALDI-MSI revealed the spatiotemporal intra-tumoral distribution of the essential aromatic amino acid phenylalanine and its de novo synthesized metabolite tyrosine. It is important to mention

that this study is based on a previous study [81] where the same mice were used but which focused on the liver. Moreover, the plasma data from the same mice provided the additional value of inter-organ metabolism ($^{13}C_6$-Tyrosine was subsequently transported to the tumor tissue after a hepatic Phe-to-Tyr conversion). **Chapter 5** hence gives evidence for the potential of studies that involve different organs together with plasma from the same individual to not only obtain a better understanding of the systemic nature of diseases, but also for improving animal welfare by achieving the highest research value by using as much material from a subject as possible. It is important to mention the widespread international 3R-concept (Replacement, Reduction, Refinement) for studies involving the use of animals [479] which aims at minimizing the number of animals while maximizing animal welfare and quality of research. Therefore, the preclinical studies conducted in the current thesis point out the noteworthiness to give a more comprehensive and valuable answer to a scientific question with a limited number of animals.

Socio-economic relevance

My PhD research projects mainly focused on atherosclerosis, cancer and wound healing. Among them, atherosclerosis and cancer are the two main dominant causes of deaths all over the world [480]. Patients with atherosclerosis and cancer are strongly affected both physically and mentally. Along with illnesses, patients and their families, caregivers and the social security system are also suffering economically from long-standing treatment expenses. Also wound healing and its care constitute another major source of total healthcare budget [481]. There are many health consequences of failed wound healing, such as infection, septicaemia, osteomyelitis, chronic morbidity or even mortality [482]. Moreover, there is a pronounced demand for wound care products in the wound-dressing markets.

Metabolomics-based preclinical studies on these diseases in this thesis could point to potential new treatments, which might merit further translational studies in humans, as well as greatly save the screening time and funding needed in clinical trials. Moreover, it might indirectly alleviate economic burden for patients and society, as well as improve quality of life for patients in the long run. For instance, in **chapter 2**, several specific lysolipids were found exclusively localized in the atherosclerotic aorta plaque. Diagnostics could benefit from this study for targeting these lipids using nuclear medicine and molecular contrast agents. Likewise, the metabolic alterations induced by high cholesterol and high fat diet observed in the **chapter 3** could inspire fitness enthusiasts, nutritionists, food industry and medical doctors. For example, a healthy diet plan with less cholesterol and fat could be strongly recommended for fitness enthusiasts, clients of nutritionists, as well as patients and their caregivers. Additionally, food manufacturers and marketers could provide healthier food products for public health and help customers make health choices. In similar fashion, the findings from **chapter 4** might bring a big value for wound-dressing markets. Similarly, the amino acids metabolism research in **chapter 5** might have a great impact for targeted delivery of therapeutics in cancer.

More broadly speaking, the strategies developed in this thesis could also be applied to other health conditions such as current coronavirus disease 19. Coronavirus patients show varying levels of severity in lung tissues and MSI-based local metabolomics could be used to identify specific metabolic signatures, and thus predict the consequence of the disease with a higher level of certainty. A subsequent successful application of potential metabolomics-based markers could dramatically reduce the test cost (e.g. point-of-care testing) and assist clinicians in prognosis evaluation. Likewise, similar approaches could also apply to other different settings or fields. For example, toxicology, which shows great interest for many pharmaceutical companies, MSI could aid in assessing the metabolic effects of potential drug candidates before clinical trials. In addition, the metabolomics-based strategies can also be used for examination of phenotypic changes in genetically modified products for public consumption in agriculture and food field. Moreover, it might also confer a powerful tool to investigate metabolomics alterations induced by global issues such as environmental pollution, and mental health problems.

Lastly, across my PhD projects, I mainly worked with MALDI-MSI instruments from Bruker Daltonics (Bremen, Germany). In the meantime, I was also responsible for the maintenance of one of Bruker Daltonics' flagship MALDI-MSI instruments (rapiflex) in the lab. Thus I had the privilege of working with Bruker Daltonics for trouble shooting, as well as giving feedbacks to Bruker Daltonics in order to improve their instrumental performance. This extraordinary experience allowed me to improve my knowledge and insight from both a scientific researcher's perspective as well as from a commercial viewpoint.