Tissue-type instrument. LipostarMSI and in-house ChemomeTricks toolbox for MALAB software were used for data processing and analysis.

For bottom-up proteomics experiment (n̂ = 10; n̂ = 10), proteins were extracted, separated using SDS-PAGE and digested prior to liquid chromatography separation; coupled to an orbitrap MS Q-Exactive HF mass spectrometer. Proteome Discoverer, enrichR and Reactome software were used for data processing and analysis.

**Results:** MALDI-MSI showed overall differences between OA and OA/TD2 patients based on their specific lipidomic profiles. In particular, sphingomyelin and phosphatidylcholine species were significantly more abundant in OA patients whereas lysolipids such as lysophosphatidylcholine species were mainly present in OA/TD2 patients, providing therefore phenotype-specific OA molecular panels. Additionally, we observed that phosphatidylcholine and sphingomyelin species were more present in the superficial layer of the cartilage whereas lysophosphatidylcholine species were more abundant in the deep layer (Fig. 1A, B). Proteomics experiments applied on cartilage enables the quantification of 114 proteins. Among those, 73 were overexpressed in OA samples whereas 41 were overexpressed in OA/TD2 patients. Among the differentially regulated proteins (Fig. 1C), phospholipase A2 was increased in the diabetic cohort, in line with the elevated level of lysolipids found in the imaging data. Our results also involved the fatty acid omega oxidation and the fatty acid biosynthesis pathways as relevant to explain this deregulation of the lipid metabolism.

**Conclusion:** MALDI-MSI combined with proteomics experiments showed different profiles between OA and OA/TD2 patients and could be employed for patient classification.

**References:**


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