Spatial multiomics show lipid metabolism alterations in prostate cancer

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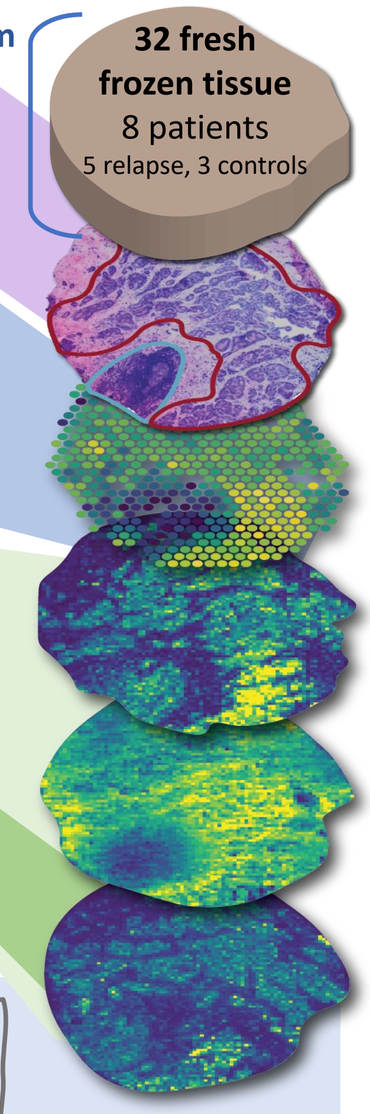
Background: Altered lipid levels and metabolism is commonly observed during prostate cancer progression. However, prostate tissue has a **heterogeneous composition**, and analysis is therefore challenging. Molecular imaging pose a significant advantage to bulk analysis by conserving the spatial location of molecules. Furthermore, combining **multiple -omics methods** together, such as metabolomics, lipidomics, proteomics and transcriptomics, is a powerful approach to profile lipid metabolism in prostate tissue.

Aim: **To map lipid metabolism in human prostate cancer tissue with spatial multiomics analysis**



Histopathology: Assessed by two uropathologists on the same sections as ST. Tissue areas were annotated as either cancer (grade group (GG) 1-5), normal glands, stroma or lymphocytes. For this study, **normal gland was compared to cancer glands**.

Spatial transcriptomics (ST): The RNA-seq based 10X kit was used for spatial gene expression (GE). ST spots (Ø50 µm, 100 µm apart) were assigned into the dominant histology tissue type and each spot was normalized based on cell-count. Normal gland spots (n=5210) were compared to cancer gland spots (n=6293).

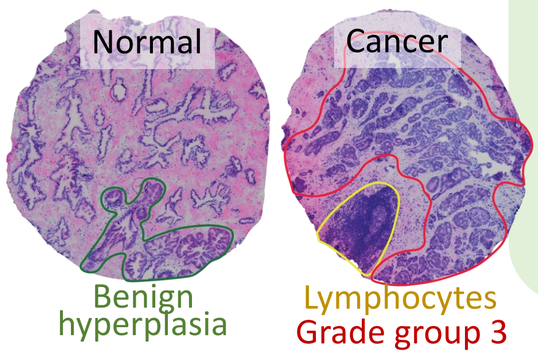
Spatial lipidomics and metabolomics: Matrix assisted laser desorption/ionization time-of-flight mass spectrometry imaging (MALDI-TOF MSI) was applied to detect small metabolites and phospholipids in both positive and negative ion mode using spatial resolution of 30 µm.

Sterols: MALDI-2 TOF MSI, an advanced method of MALDI MSI, allowed for sterol detection in positive ion mode.

All serial sections were 10 µm thick

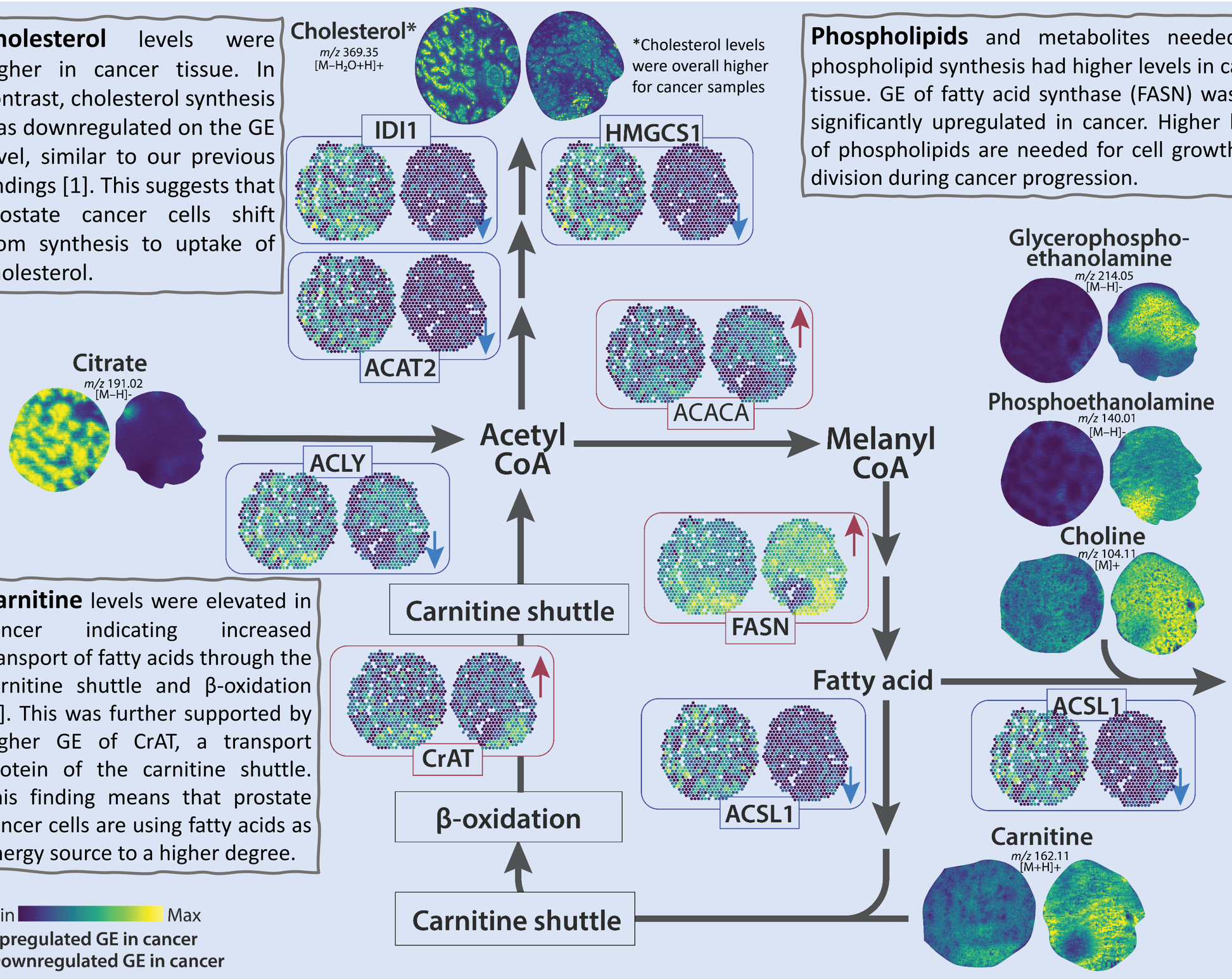
Results & Discussion

Main findings are represented through one normal and one cancer sample, and shows alterations of **phospholipids, cholesterol metabolism** and **β-oxidation**

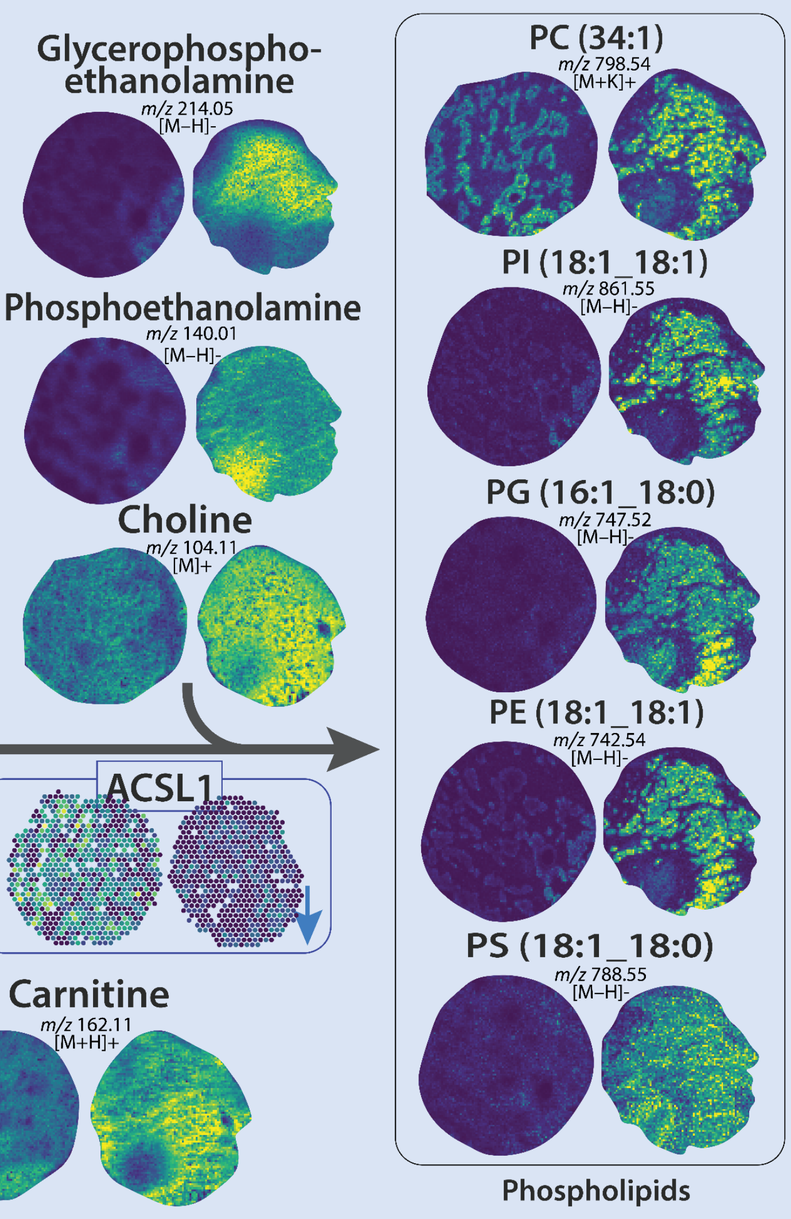


Cholesterol levels were higher in cancer tissue. In contrast, cholesterol synthesis was downregulated on the GE level, similar to our previous findings [1]. This suggests that prostate cancer cells shift from synthesis to uptake of cholesterol.

Carnitine levels were elevated in cancer indicating increased transport of fatty acids through the carnitine shuttle and β-oxidation [2]. This was further supported by higher GE of CrAT, a transport protein of the carnitine shuttle. This finding means that prostate cancer cells are using fatty acids as energy source to a higher degree.

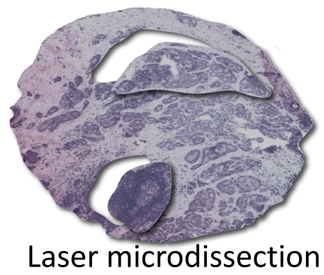


Phospholipids and metabolites needed for phospholipid synthesis had higher levels in cancer tissue. GE of fatty acid synthase (FASN) was also significantly upregulated in cancer. Higher levels of phospholipids are needed for cell growth and division during cancer progression.



Conclusion & future work

These preliminary investigations clearly demonstrate changes in lipid metabolism in heterogenous prostate cancer tissue. Spatial multiomics is a particularly powerful approach to understand the role of lipids in prostate cancer progression. Recently retrieved LMD proteomics data from the same samples will further create a wholesome picture of lipid metabolism. We will map the associations between lipid metabolism to clinical cancer progression, the different grade groups and find potential roles of the tumor microenvironment by analyzing the large ProstOmics cohort of 498 samples from 114 patients.



Laser microdissection (LMD) proteomics
At least 50 lipid relevant proteins detected

References

[1] Rye, M.B., *BMC Cancer* **18**, 478 (2018)

[2] Andersen, M.K. *Cancer Metab* **9**, 9 (2021)

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