Integrating Spatial Metabolomics and Spatial Transcriptomics on the Same Cancer Tissue Sections to Detect Gene-Metabolite Correlations

Trevor Godfrey[1], Yasmin Shanneik[1], Wanqiu Zhang[2], Thao Tran[2], Nico Verbeeck[2], Nathan H. Patterson[2], Faith Jackobs[1], Chandandeep Nagi[3], Maheshwari Ramineni[3], Livia S. Eberlin[1]

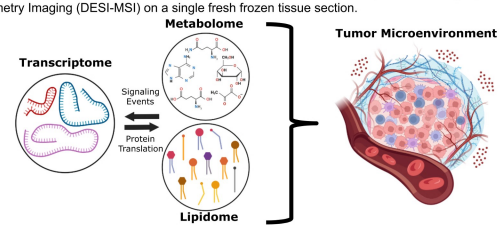
[1]Department of Surgery, Baylor College of Medicine, Houston, TX, 77030, USA. [2]Aspect Analytics NV, Genk, Belgium. [3]Department of Pathology and Immunology, Baylor College of Medicine, 77030, Houston, TX, USA

Overview

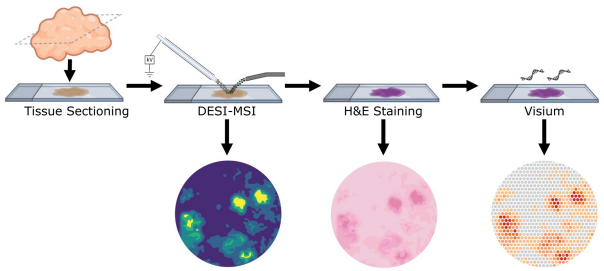
- A workflow named DESI+ST was designed to combine Desorption ElectroSpray Ionization Mass Spectrometry Imaging (DESI-MSI) and Visium Spatial Transcriptomics (ST) on the same tissue section.
- The DESI+ST workflow was shown to have almost no negative impact on RNA integrity and spatial sequencing quality.
- DESI+ST was performed on six human cancer samples.
- Integration of Visium-ST and DESI-MSI data reveals strong, unambiguous, spatial correlations of metabolomic and transcriptomic information in human cancer tissues.

Introduction

- The relationship between the metabolome and the transcriptome plays a vital role in understanding the tumor microenvironment.
- Spatial transcriptomics (ST) and Mass Spectrometry Imaging (MSI) spatial metabolomics techniques have made strong contributions of the mapping of the tumor microenvironment.[1-2]
- Data from ST and MSI has previously been integrated by analyzing separate serial sections.[3-5]
- Combination of ST and MSI on the same tissue section would minimize section variability and increase capacity to correlate metabolic and transcriptomic heterogeneity.[6]
- We have developed a workflow that combines Visium-ST with Desorption ElectroSpray Ionization Mass Spectrometry Imaging (DESI-MSI) on a single fresh frozen tissue section.



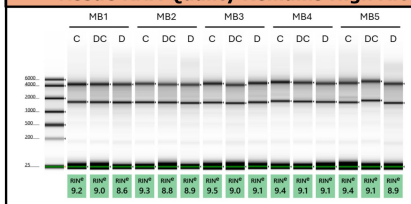
Methods

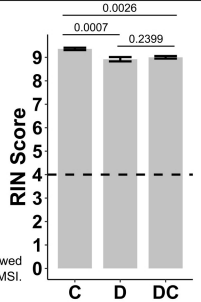


- 6 Human Cancer Samples (3 lepidic lung adenocarcinoma, 3 invasive lobular breast cancer) were analyzed with the Desium workflow.
- Serial sections for two samples were analyzed with only the Visium protocol as a control.
- DESI-MSI Parameters: samples analyzed in negative ion mode on a Xevo G2-XS QTOF mass spectrometer (Waters) with 100% Methanol on a DESI-XS stage at 100 µm spatial resolution.
- Visium CytAssist Protocols: CG000614 and CG000495
- DESI-MSI and Visium-ST data were coregistered, and granularity matching between data formats was performed using a gaussian weighting algorithm.

Results

Tissue RNA Quality Remains High After DESI-MSI



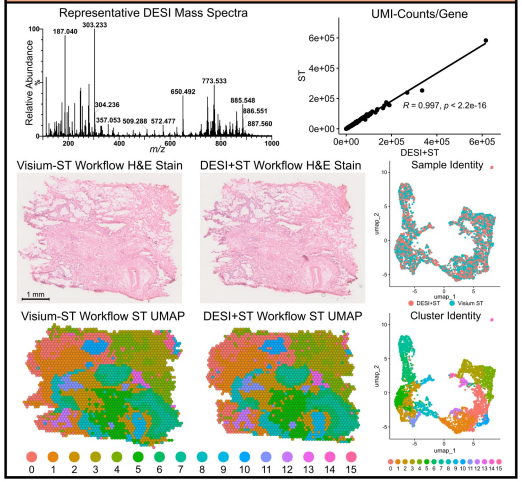


MB: Mouse Brain, C: Control Serial Section, DC: DESI Control (tissue section left at room temperature for 1.5 hour), D: 1.5 hour DESI Image with 100% methanol spray solvent

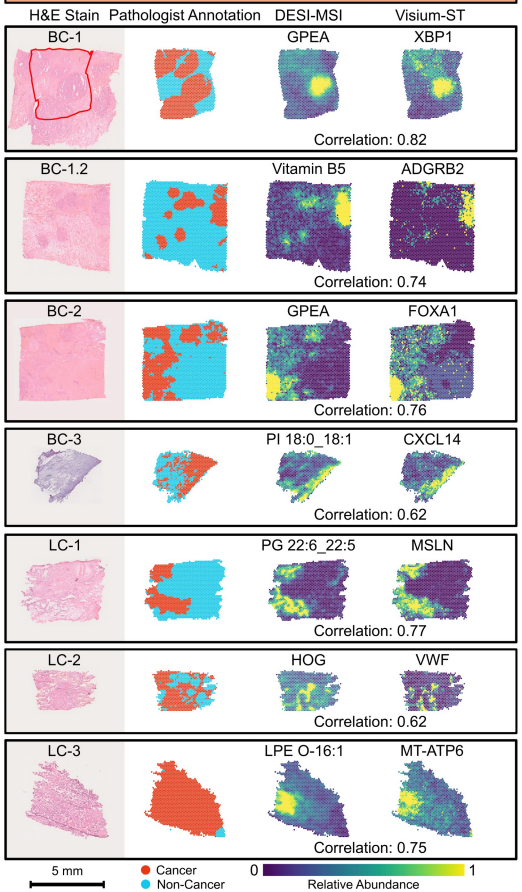
Tests on the effects of DESI-MSI on RNA quality of five mouse brains showed almost no change in RNA quality as shown by high RINe Scores after DESI-MSI. Minimum RIN of 4 is required for Visium-ST.

Results

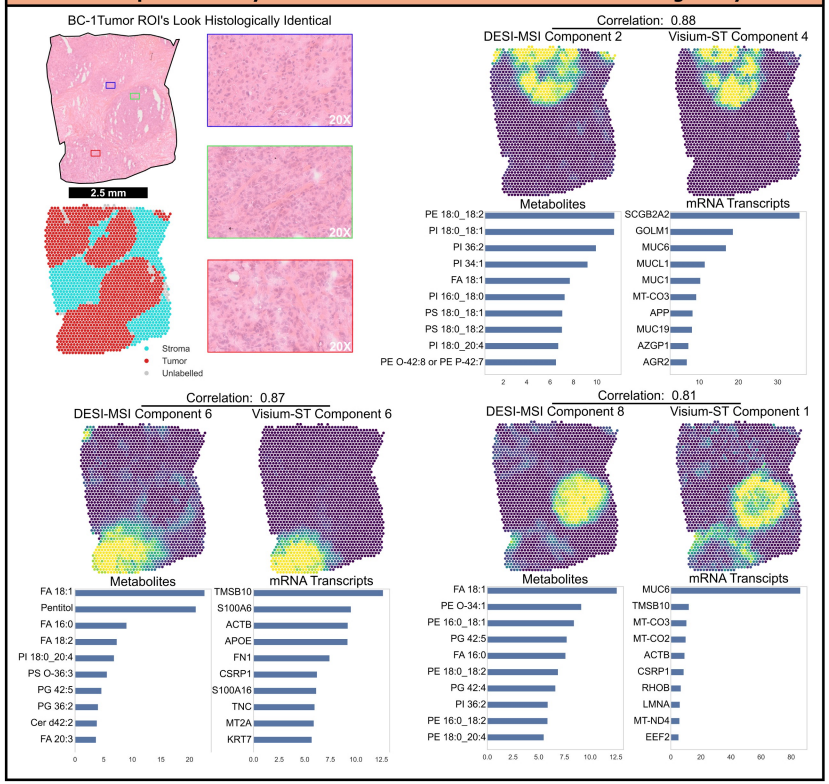
DESI-MSI and ST Data are Unaffected by DESI+ST Workflow



DESI+ST Reveals Correlations Between RNA and Metabolites



Component Analysis of DESI+ST Reveals Intra-tumor Heterogeneity



Conclusions

- Performing DESI-MSI before Visium-ST has almost no impact on RNA and Visium-ST data quality.
- Transcriptomic and metabolomic data display strong spatial correlations one with another, 6,075 Gene-Metabolite correlations with a magnitude above 0.5 were identified with DESI+ST.
- Component analysis of DESI+ST data reveals intra tumor heterogeneity not visible with histology alone.
- The DESI+ST workflow allows for precise alignment of metabolomic and transcriptomic data from the same tissue section.

Future Directions

- Cell deconvolution of Visium-ST data to compare metabolite distributions by cell type.
- 5-10 µm DESI-MSI with Visium HD to perform high resolution DESI+ST.

Acknowledgements

- Thanks to the Gordon and Betty Moore Foundation for funding and support.
- Thanks to Aspect Analytics for their expertise in data analysis and multimodal image coregistration.
- Intro and method figures made in BioRender, methods representative data made by Rachel Davidowitz
- COI Statement: L.S.E. is an inventor in patents related to DESI-MS imaging technology owned by Purdue Research Foundation that were licensed to Waters Corporation and receives royalties from sales of the systems. W.Z., T.T., N.V., and N.H.P. are employees at Aspect Analytics NV. N.V. is a shareholder of Aspect Analytics NV.

References

LinkedIn

Eberlin Lab Website

Aspect Analytics Website