EXPLORING CELLULAR SENESCENCE AND AGING OF THE SKIN WITH SPATIAL MULTI-OMICS.

R Haider[1,2]; S Zoratto[1,2]; NH Patterson[3]; W Zhang[3]; T Tran[3]; C Kremslehner[2,4]; G Gendronneau[2,5]; A Ly[3]; N Verbeeck[3]; F Gruber[2,4]; M Marchetti-Deschmann[1,2]

Author affiliations:
[1] TU Wien, Vienna, Austria
[2] Christian Doppler Laboratory for Multimodal Imaging of Aging and Senescence - SKINMAGINE, Vienna, Austria
[3] Aspect Analytics NV, Belgium
[4] Department of Dermatology, Medical University of Vienna, Vienna, Austria
[5] Chanel PB, Pantin, France

Introduction

The skin is the largest organ in the human body and forms the first line of defence against various environmental factors. Despite differences in function of the layers of skin, the expression and distribution of different molecules in skin and how this changes with age has largely not been investigated.

This study utilised a multi-omics approach to conduct a spatially-resolved analysis of age-related changes in the human skin transcriptome and N-glycome. Additionally, we describe tooling and a cross-modality data structure for correlative, differential, and spatial multimodal data analysis that revealed novel senescence-related changes in the distribution of N-glycans and transcripts in human skin.

Methods

Skin biopsy samples were collected from young (Female, 36y years of age) and old (Female, 69 years of age) donors. A single section was sequentially analyzed via autofluorescence, MALDI-IHC (50 µm), MALDI-FTICR MSI (Bruker) after PNGaseF digestion (50 µm), immunofluorescence, and tissue staining. Spatial transcriptomics using the Visium assay (10X Genomics) was performed on a consecutive section after autofluorescence imaging, and another section was used for 10 µm glycan analysis after autofluorescence analysis for high spatial resolution information. The Weave software platform (Aspect Analytics) was used to co-register all datasets at full resolution using a non-rigid spline-based algorithm, allowing for simultaneous viewing and integrative analysis of multiple datasets.

The advanced integration pipeline creates a common coordinate system and matches readouts that account for the differences in spatial resolutions, which enabled spatial correlation analysis across assays, multi-omics tissue segmentation and differential expression analysis. Correlation analysis was conducted to investigate differences in transcript and N-glycan distribution patterns between younger and older donor samples.

Results

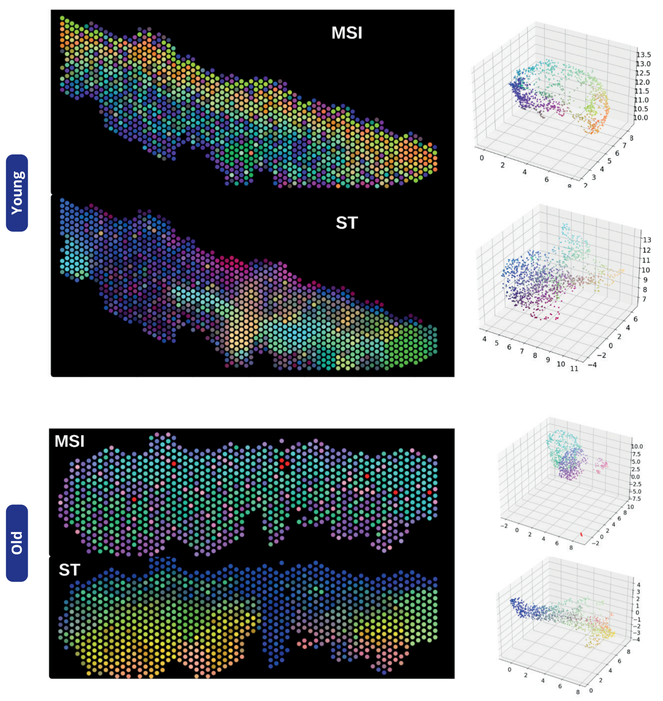

Fig. 1: 3D UMAP visualization of co-registered and matched MSI and (spatial transcriptomics ST) datasets in young (top) and old (bottom) samples. When UMAP embeddings are projected onto tissue locations, it is possible to see clear stratification in the MSI-measured younger sample. However, this stratification is less apparent in the older MSI-measured sample.

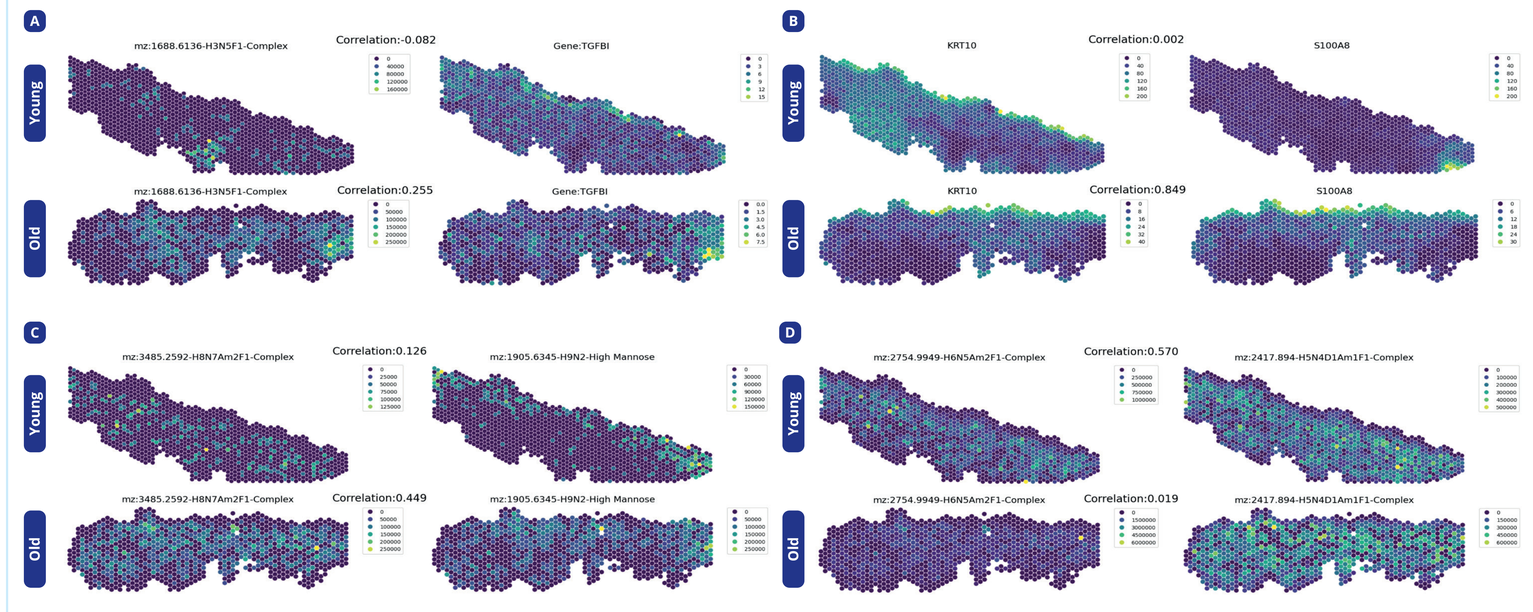

Fig. 3: Visualization of differently spatially correlated pairs across young and old skin samples. **(A)** The TGFB1 gene and H3N5F1 glycan have low spatial correlation in young samples which increases with age. **(B)** KRT10 gene is highly expressed in the upper layers in young and old samples. In comparison, S100AB gene expression is increased in the upper layers with age. **(C, D)** Glycan-glycan pairs that correlate differently across young vs. old samples.

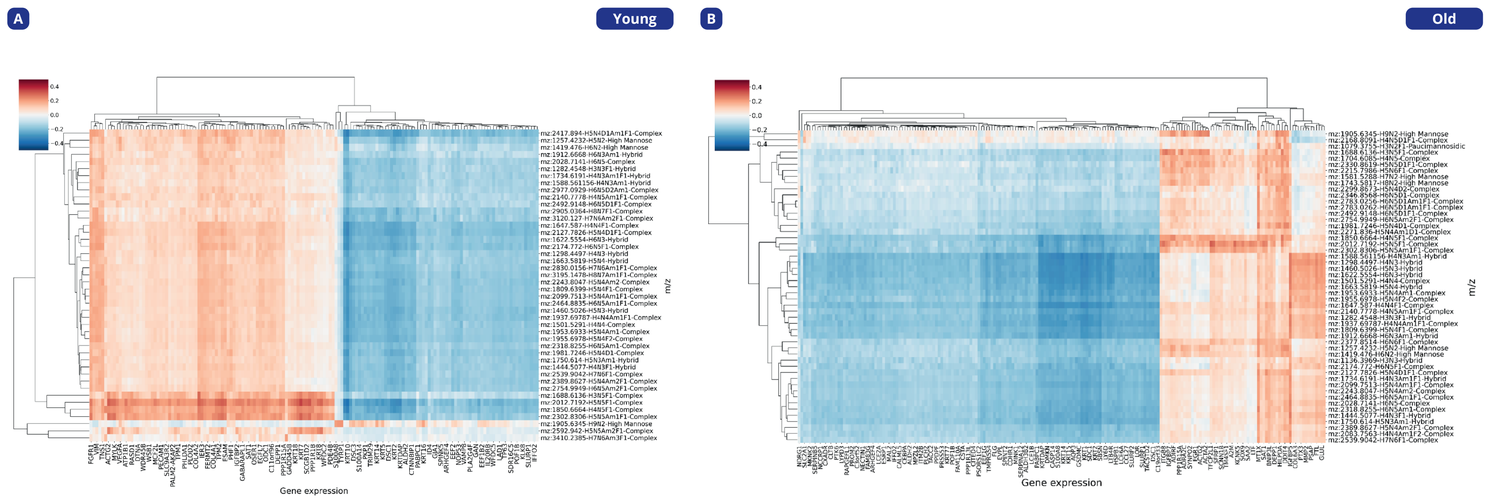

Fig. 2: Correlation heatmaps of matched MSI and ST data from young **(A)** and old **(B)** samples. Positively and negatively correlated gene - m/z pairs are shown in the bottom

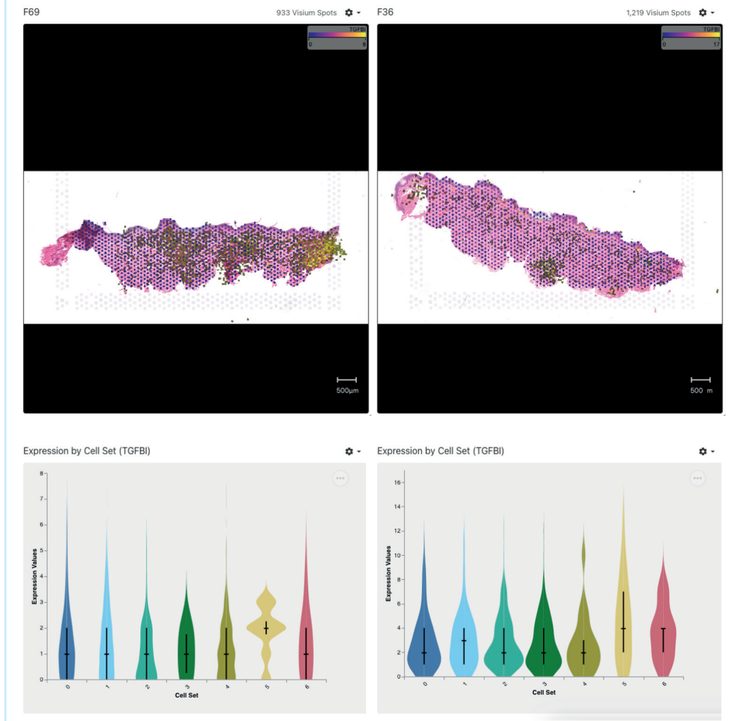

Fig. 4: Screenshot of the interactive report of this multi-sample multi-modal datasets via Weave platform. Two samples young (F36) and old (F69) are shown in the top two left panels. Two modalities are overlaid and visualized together: gene expression 'TGFBI' from spatial transcriptomics data (in plasma heatmap) and m/z peak 1688.6163 - H3N5F1 from MSI data (in yellow). This gene - glycan pair has a positive spatial correlation (coefficient: 0.255) in the old sample, but this relationship is not present in the young sample (coefficient: -0.082). Leiden clustering was performed on joint Visium data from both young and old samples.

Conclusion

- Multimodal Imaging of skin tissue sections shows differences in the distribution of N-glycans and transcripts associated with age.
- Differential spatial correlations could be found for gene-gene, glycan-glycan, and gene-glycan pairs that vary with age of the sample donor.
- A web-based report allows simultaneous co-visualization and exploration of the distribution of gene transcripts and N-glycans, as well as clustering results across samples based on transcriptomics.

AGENTSCHAP INNOVEREN & ONDERNEMEN · Vlaanderen is ondernemen · Horizon 2020 · FLANDERS INVESTMENT & TRADE · Flanders State of the Art