ImaBiotech
Revealing Biological Secrets

APPLICATION NOTE

UNRAVELING DISEASE COMPLEXITY WITH INTEGRATED SPATIAL SYSTEMS BIOLOGY APPROACH

Interrogate complex biological systems through spatially-defined quantification of numerous biomolecules.

System biology involves complex biological organization and processes in terms of molecular constituents ordered in many interconnected pathways. A holistic approach is critical to our understanding of the complexity of disease and the relationship among drug targets-disease. Changes in molecular pathways can be detected using high-throughput omics methods such as transcriptomics, proteomics, metabolomics and integration of multiple omics datasets which is becoming key to revealing novel biological insights. In this perspective, we highlight the use of an image based multi-omics integration approach to unravel information flow and mechanisms during complex biological events.

APPROACH

Here, we describe a multimodal approach by allowing the parallel spatially-defined quantification of biomolecules. Our newly developed workflow allows *in-situ* comprehensive molecular architecture and phenotypes analysis that have eminent potential to classify disease according to their distinct characteristics. The workflow includes the import and the overlay of a molecular image obtained from a tissue section analyzed by Quantitative Mass Spectrometry Imaging (QMSI) onto an adjacent tissue section prepared for GeoMx™ Digital Spatial Profiler (DSP) analysis (Figure 1) with fluorescent morphological makers. The selection of the regions of interest (ROIs) on the GeoMx DSP is then based on the molecular signal provided by the QMSI analysis. This way the subsequent protein/gene expression analysis can be directly linked to a pertinent metabolic activity and allow the accurate understanding of the interplay between biomarkers within the complexity of a disease.

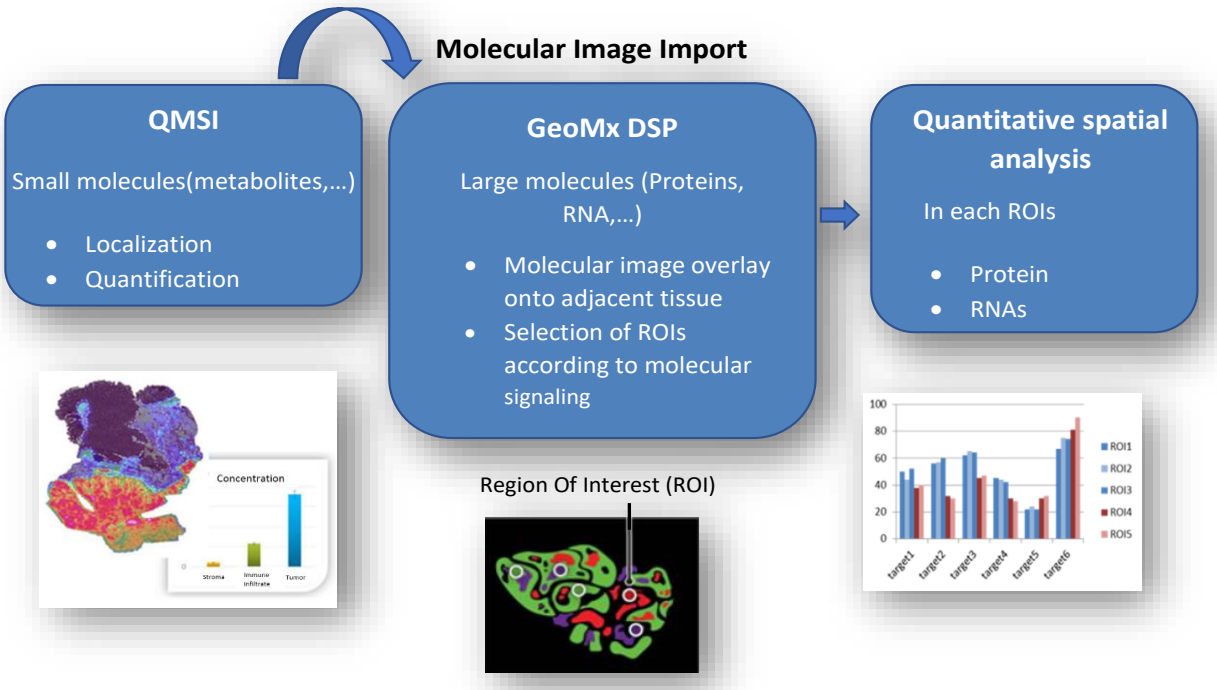

Figure 1: Spatial multi-omics workflow

CASE ILLUSTRATION STUDY

Here we report an example of lactate distribution derived from the analysis of a PDX tissue section by QMSI (Figure 2B). The lactate accumulation in this tissue section was highlighted in red and showed an heterogenous distribution along the tissue section. The overlay of the molecular image with the Hematoxylin-eosin (H&E) staining (Fig 2A) on an adjacent tissue section clearly showed that the lactate mostly accumulates in the different tumor regions of the PDX model (Figure 2C). The concentration of lactate within the different tumor regions was also heterogenous.

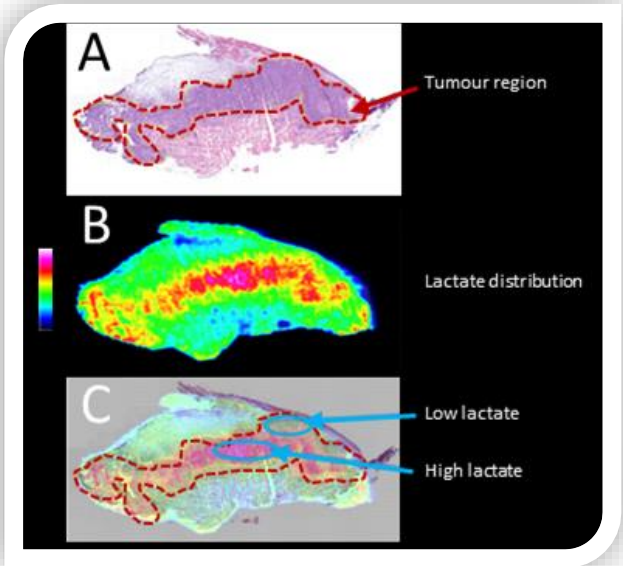

Figure 2: A- H&E staining of PDX model for histopathology defined localization of the tumor segment. B- Distribution of lactate in PDX model. C- Overlay of the molecular image with the H&E staining for histopathology-defined localization of the metabolite across the tissue section.

The QMSI-H&E overlay image was then imported into the Geomx DSP device and further aligned to the fluorescently labeled adjacent tissue section. The fluorescent morphologic markers delimitated the tumor (panCK) versus the stroma content (CD45). The alignment between the QMSI-H&E and the fluorescent image was manually performed and once both images were correctly aligned (Figure 3A), the ROIs for protein/RNA analysis were delineated based on the QMSI signal. The drawn ROIs corresponded to the tumor regions with different lactate accumulation (Figure 3B).

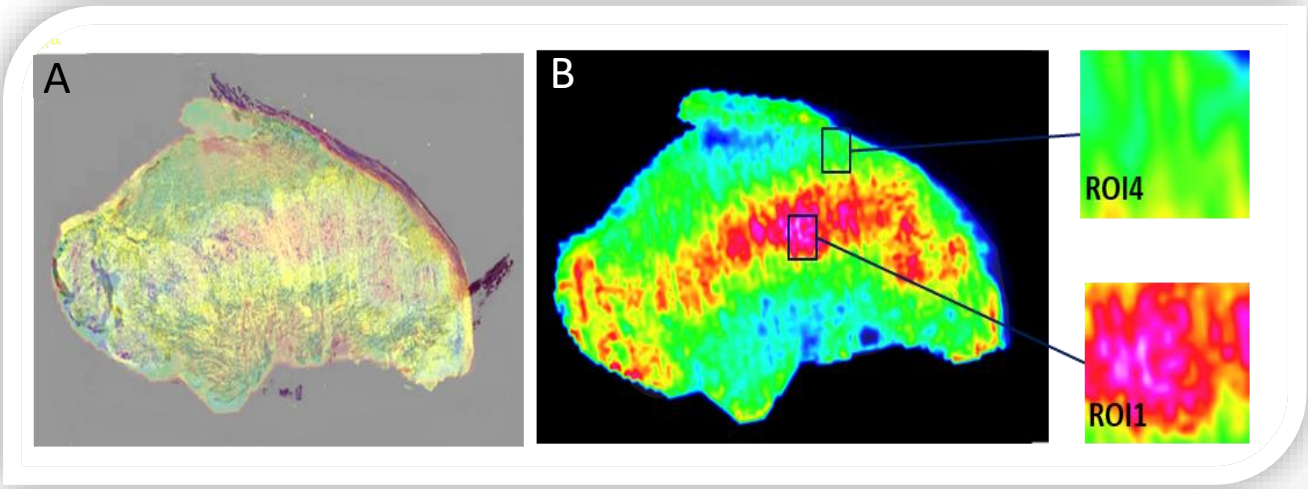

Figure 3: A- H&E-QMSI image overlaid with fluorescently labeled image after alignment. B - ROIs were delineated based on QMSI signal. ROIs corresponding to highest lactate concentration and lower lactate concentration were designed, i.e., ROI1 corresponded to high lactate and ROI4 corresponded to low lactate.

Proteins were then quantified from each selected ROIs. Figure 4 showed the expression profile of some of the protein targets within different ROIs corresponding to high lactate and low lactate concentration. The expression profile exhibited a differential protein expression that was dependent on the concentration of lactate. They were low expressing T cell markers in the high lactate regions showing that in these regions the T cell population were depleted.

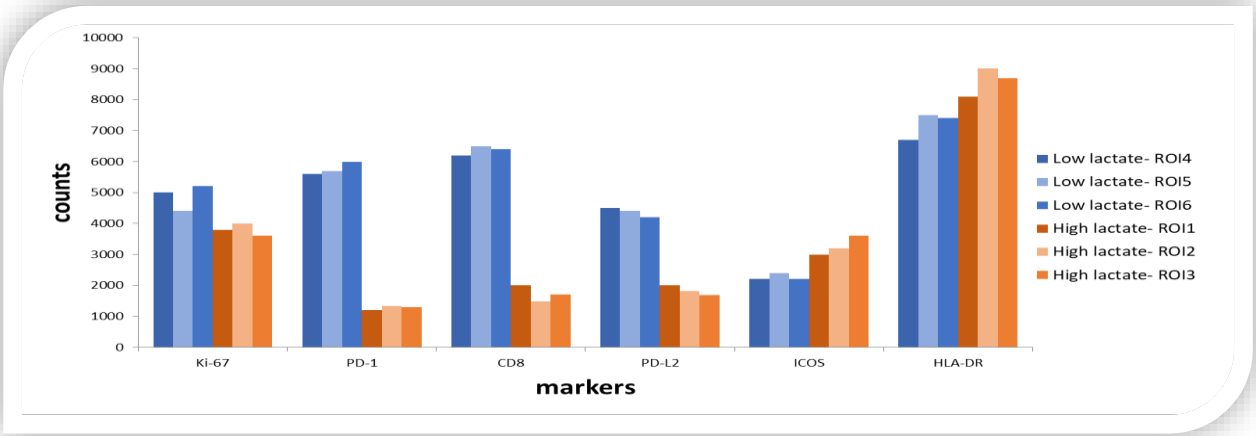

Figure 4: Comparison of the protein expression of several target proteins in high-concentrated and low-concentrated lactate regions

APPLICATIONS

Deciphering the molecular complexity at the spatial level within the tissue context remains one of the prerogatives to understand the heterogeneity of the mechanisms that give rise to various disease states and how cells interact with each other to help identifying therapeutics pathways for new treatments.

The limitations of current tools due to their inability at providing spatial information and their cumbersome workflow for understanding heterogeneity inhibit personalized medicine and the discovery of advanced therapeutics. In fighting diseases like Alzheimer's, diabetes and cancer, the proposed methodology by correlating the spatial information in tissue morphology with multi-omics allows to:

- Probe the more complex and transient molecular changes that underpin the course of the disease and response to treatment
- Help select the right drug target

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