Spatial Multi-Omics Meets AI:
Turning Tissue into Actionable Insight

Designing Insightful Spatial Multi-Omics Studies: From Sample to Signal

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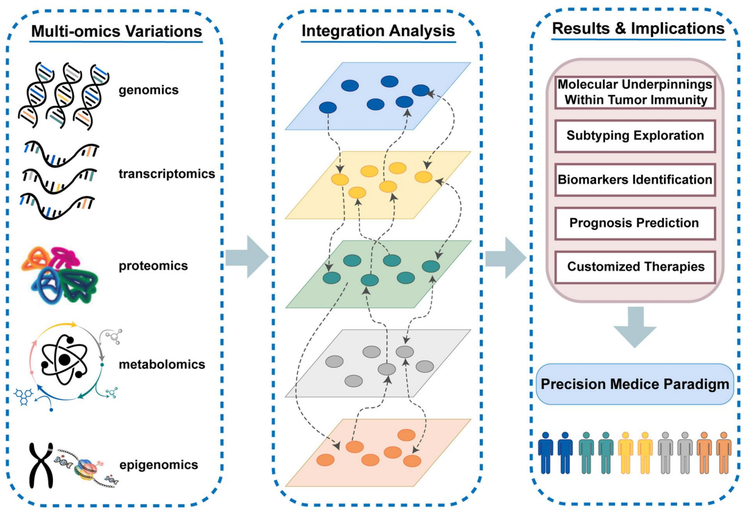
BACKGROUND

Precision medicine requires technologies capable of capturing both molecular heterogeneity and tissue architecture. Unlike conventional bulk approaches, spatial multi-omics preserves tissue context, enabling the characterization of genes, proteins, metabolites, and cell–cell interactions within their native environment. Combined with AI-driven image analysis and multimodal data integration, spatial multi-omics provides a powerful framework for biomarker discovery, patient stratification, and treatment response prediction.



OBJECTIVE

To demonstrate the potential of AI-enabled spatial multi-omics for precision medicine, we applied an established machine learning framework to identify treatment-associated molecular signatures in cervical cancer using integrated proteomic, transcriptomic, and metabolomic data.

METHOD

Study Cohort

The study cohort consisted of 22 patients with cervical cancer undergoing immunotherapy. Patients were stratified according to clinical outcome into responder (R) and non-responder (NR) groups.

Spatially resolved multi-omics profiling was performed on Tumor and Tumor-Stroma Interface regions of interest (ROIs) selected from each tissue specimen. Three complementary molecular layers were analyzed: proteomics, transcriptomics and metabolomics.

Responder R (n = 8)
Non-Responder NR (n = 14)

ROIs	Tumor	Interface
Total	44	50
NR	*31*	*23*
R	*13*	*27*

Omics	Features
Transcriptomic	11202 genes
Proteomic	5 proteins
Metabolomic (+)	2254 m/z
Metabolomic (-)	2548 m/z

Data Integration and Machine Learning Pipeline

A multi-omics integration workflow was implemented using DIABLO (Data Integration Analysis for Biomarker Discovery using Latent Variable Approaches for Omics Studies), a supervised, N-integration method framework from the mixOmics package.

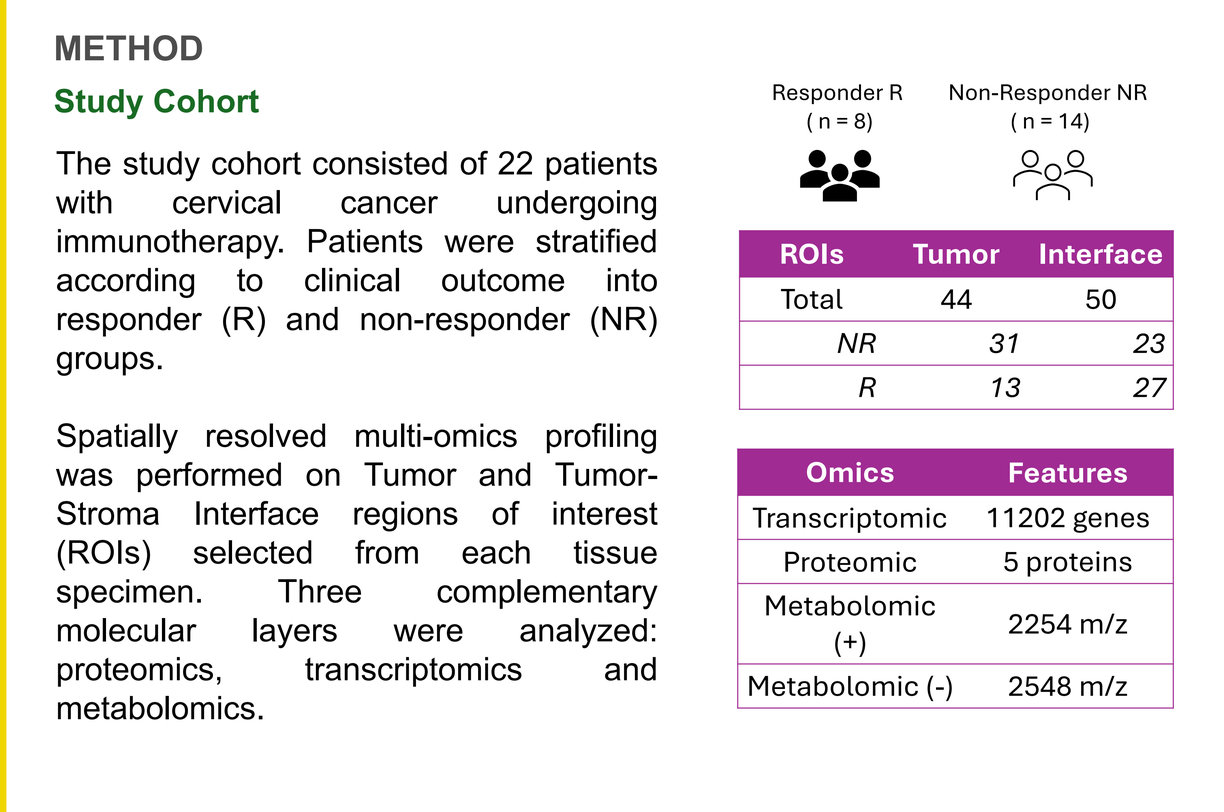


FIGURE 1. DIABLO-based multi-omics analysis workflow. Omics data were preprocessed to improve data quality and comparability across modalities. DIABLO was then used to integrate the different molecular layers and identify treatment response-associated signatures. Model performance was evaluated by cross-validation, while downstream analyses focused on sample discrimination, key biomarkers, and feature correlations.

To preserve the spatial context of the tissue, data integration was performed at the ROI level rather than at the patient level, enabling the incorporation of spatially resolved molecular information into the analysis. Tumor and Tumor-Stroma Interface regions were investigated independently, allowing the identification of compartment-specific molecular signatures and the comparison of distinct biological microenvironments. Model performance was assessed using cross-validation procedures.

RESULTS

The DIABLO multi-omics model successfully discriminated responders from non-responders in both Tumor and Tumor-Stroma Interface regions, achieving classification error rates ranging from 0.14 to 0.27 and AUC values between 0.86 and 0.93.
Across molecular modalities, transcriptomic and metabolomic data contributed most strongly to patient stratification, whereas the proteomic layer displayed lower discriminative power, likely due to the limited number of measured biomarkers. Feature selection identified key response-associated genes, including *IDO1*, *WARS1*, *TAP1*, *HLAE*, *CCL5*, *FOXP3*, and *FOXO3*, highlighting the importance of immune-related pathways in shaping therapeutic outcomes.

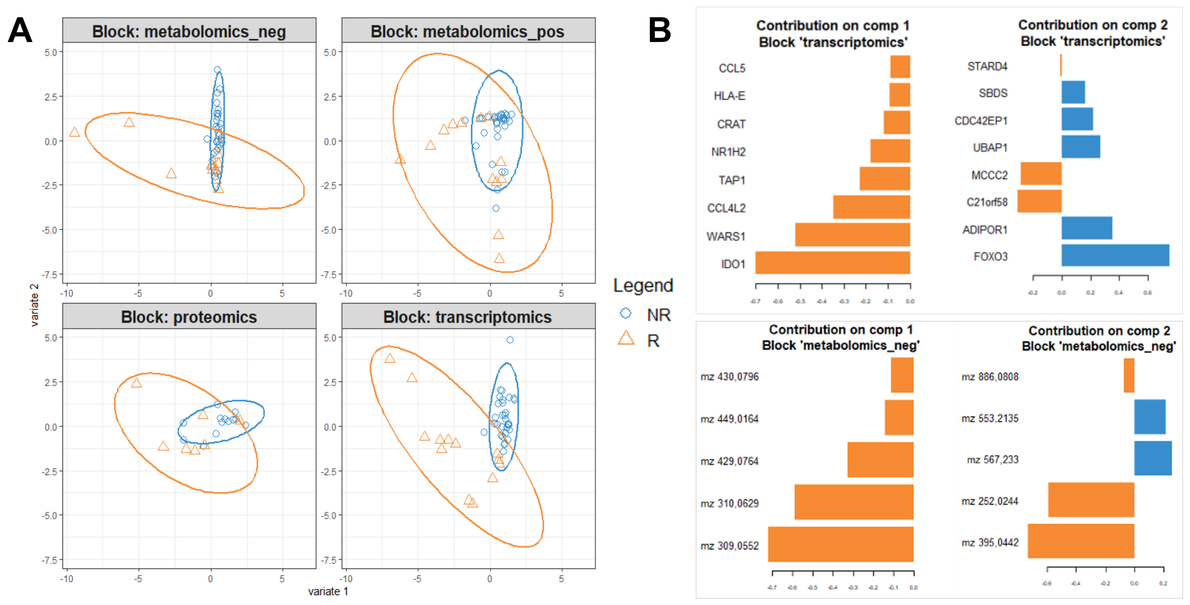


FIGURE 2. A- DIABLO sample projections of responders (R) and non-responders (NR) across transcriptomic, proteomic, positive-ion and negative-ion metabolomic data from Tumor ROIs. **B-** Contribution of the most features to Component 1 (left) and Component 2 (right) in Tumor ROIs.

In addition, correlation analysis identified coordinated expression patterns, notably between *IDO1* and *WARS1*, suggesting shared biological mechanisms potentially linked to interferon signaling and immune regulation. Together, these findings demonstrate that spatial multi-omics integration can uncover biologically meaningful molecular signatures associated with treatment response in cervical cancer.

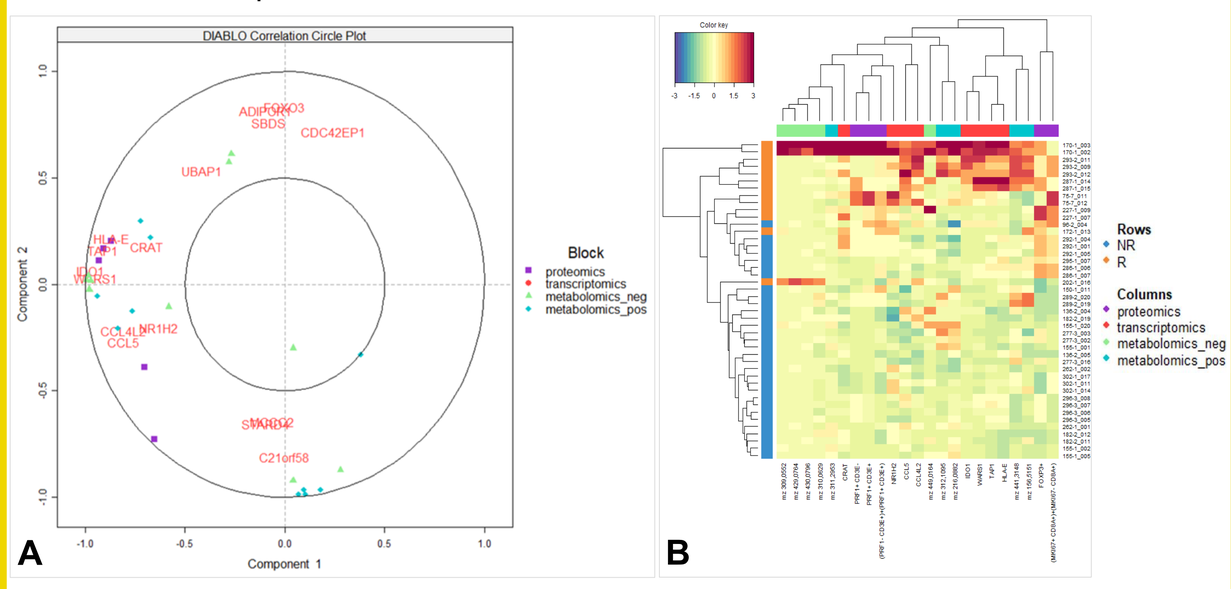


FIGURE 3. A- Correlation circle of the most discriminative multi-omics features identified by DIABLO in Tumor ROIs. **B-** Clustered heatmap of treatment response-associated multi-omics features across Tumor ROI samples, highlighting molecular similarities and differences between responders and non-responders.

CONCLUSION

AI models, when trained on spatial omics data, can more accurately predict treatment responses by analyzing the spatial arrangement and molecular states of cells. This allows for precise identification of patient subgroups most likely to benefit from specific treatments. By integrating AI and spatial omics early in drug development, companies can better predict treatment efficacy, thus reducing late-stage trial failures and improving clinical success rates.

Singh A, Shannon CP, Gautier B, Rohart F, Vacher M, Tebbutt SJ, Lê Cao KA. DIABLO: an integrative approach for identifying key molecular drivers from multi-omics assays. Bioinformatics. 2019 Sep 1;35(17):3055-3062. doi: 10.1093/bioinformatics/bty1054. PMID: 30657866; PMCID: PMC6735831.