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COMMENTARY

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Connecting the cell-type-specific microenvironment dynamics and function of organism through multimodal spatial omics profiling

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Emerging spatially resolved omics techniques enable profiling the complex cell types, and cellular functional regulation and molecular intercommunications while preserving the native cellular organizations from various tissue slices. It reveals the "structural heterogeneity" from multiple perspectives and exploring the potential physiology and pathology mechanisms at the cellular and molecular levels. Accurately identifying cells that possess the common the spatial arrangement and the associated molecular characteristics from the same or distinct sources across the multiple tissue slices, is essential to spurring the data analysis across the spatial omics.[1] Existing spatial alignment processing only works for the homogeneous alignments, such as, the same status slices or 3D organ reconstruction from serial slices, and struggle to handle the heterogeneous slices involving the uneven spatial resolution, non-rigid deformations, and batch effects. As such, connecting the cell-type-specific microenvironment dynamics with functional annotations through cross-spatial omics data provide an opportunity to promote the understanding of cell-cell organization, organ function and disease mechanisms (Figure 1).

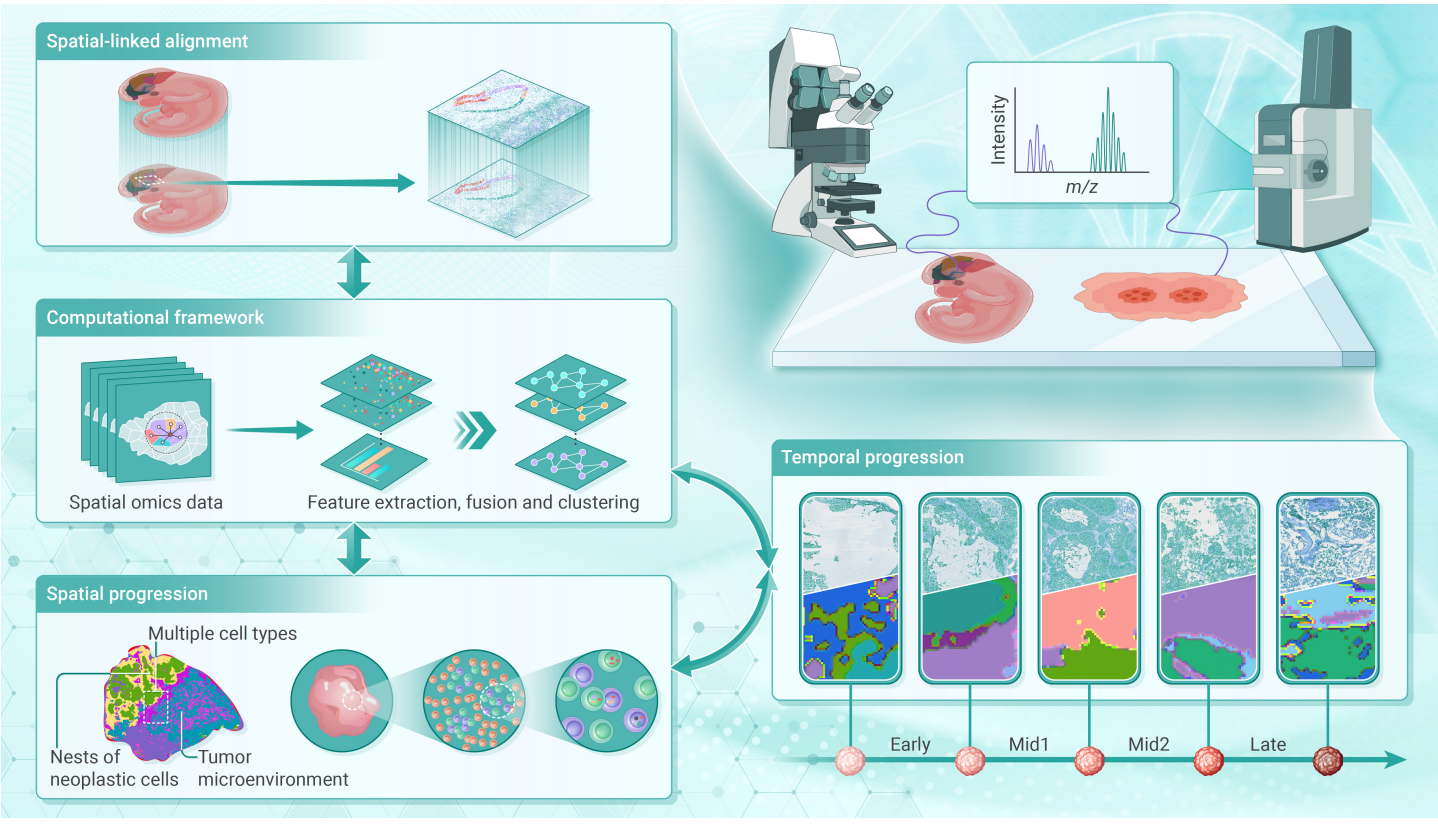

Figure 1. Multimodal spatial omics profiling for tumor progression and embryonic development.

From the view of detected information, spatial omics mainly comprises five branches, namely, spatial genomics, spatial epigenomics, spatial transcriptomics, spatial metabolomics, and spatial proteomics. These revolutionary approaches offer the opportunity to delineate the molecular landscapes across multiple length scales from single cell to intact organ under both physiological and pathological status. With the advancement of artificial intelligence, current research increasingly emphasizes both the extremely microscopic and macroscopic levels, as well as data correlations driven by big data and large-scale models, facilitating multi-factor and multi-parameter interactions and synergies.[2] However, foundational aspects and standards for parametric models remain unresolved, which represents a critical gap in current development. Additionally, prior to developing artificial intelligence algorithms, it is essential to fully consider tissue-specific microstructural information, its correlations, potential interactions, and causal mechanisms, rather than completely relying on algorithmic or big-data computational approaches.

SPATIAL STRUCTURE-FUNCTION SYNERGY

Tissue structure at sub-organ/areas level and its function possess the intrinsic relationships. As a representative tissue with extremely strong heterogeneity, the interaction between tumor cells and their microenvironment is a critical driver of tumor progression and metastasis. Tumor and its micro-area display distinct diversity of spatial information depending on the spatial organization of diverse cell populations within the tissue architecture.

Tumor cells experience multiple environmental stresses imposed by their location and microenvironment. More importantly, tumor cells adapt to specific niches within the local tumor microenvironment by altering their transcriptional and metabolic programs, enabling immortality. Take the cellular metabolism as an example, highly compartmentalized in subcellular organelles occur during the metabolic dyshomeostasis or disturbance, impacting the various cellular and tissue functions. From the perspective of epithelial-mesenchymal transition, tumor cells exhibit increased physical and physiological plasticity during progression, reducing their dependence on nutrition and oxygen availability and facilitating metastasis. Hence, it is necessary to explore the change-of-state and functional networks across the (sub)-cellular compartments to distinguish molecular features (genes, proteins, or metabolites) contribute to disease-specific molecular phenotypes.

Considering the importance of cellular spatial organization mentioned above, when conducting multimodal spatial omics alignment or fusion, the spatial relations among various cell types across varying length scales are explored for investigating the effects of spatial extents in specific physiological or pathological processes. This strategy is particularly applicable to tissue slices with mismatched or overlapping feature sub-areas. The spatial relationship between cell types such as the cell-cell spatial co-localization (proximity-based interactions) and cell-cell spatial separation (distance-dependent relationships) may reveal the significant functional differences, complementarity, and crosstalk between healthy/paracancerous and diseased/cancerous tissues. Furthermore, the spatial relationships of cell types can span different length scales ranging from single-cell resolution with micron-level to (sub) organ architectures with centimeter-level.[3] For instance, certain cell types co-localize at micron scales to participate in short-range regulatory interactions and paracrine signaling; some cell types co-localize within distinct microenvironments or functional sub-areas at meso-scales (μm to mm); other cell types directly localize to macro-scale anatomical structures or sub-organ compartments (mm to cm).

TEMPORAL SERIES-FUNCTION COMPLEMENTARY

The structural composition of (sub) organs or tumors undergoes dynamic remodeling throughout their spatiotemporal developmental processes, laying the foundation for their ultimate organ structural homeostasis, functional execution, and pathological progression study. Taking embryonic development as an example, organs are complex structures composed of multiple cell types arranged in precise and orderly patterns. This precisely orchestrated cellular architecture directly dictates tissue-specific physiological functions. During organogenesis, a fundamental architecture of tissue is formed by collaborating with progenitor and differentiated cells. Using tumor progression as an example, multiple biological features within the same lesion undergo significant changes over time. These components can vary either independently of each other or in a tightly coordinated manner. Beyond the tumor cells themselves, the abundance, spatial distribution, and functional orientation of each cellular component within the tumor microenvironment change over time and space during progression, thereby further shaping intra-tumoral heterogeneity.

2D or 3D spatial omics techniques can only provide a momentary representation of molecular expression. Recent research proposes augmenting these approaches with time series data to create 4D information. This suggests longitudinally monitoring phenotypic expression over time within the same tissue specimen.[4] The continuous/dynamics spatiotemporal intercellular communication identified through spatial omics plays a pivotal role in driving organ morphogenesis (including at whole-embryo level), tissue homeostatic maintenance, and disease pathogenesis. Multiple spatial omics fusion and mutual alignment offer significant advantages over single spatial omics technique by integrating omics coverage and spatotemporal resolution. Fusing or aligning representative time points across the intact spatially dynamic procedure like the tumor metastasis, embryogenesis, facilitates acquire the molecular changes at representative time points and infer the potential molecular mechanisms. Exploring rich 3D spatial information from embryo-scale datasets and characterizing cell-cell interactions constitute both the key focus and major challenges in studying organ development. An advanced framework (Spateo) is developed to obtain a 3D spatio-temporal modeling of molecular hologram throughout the whole mouse embryo process. By utilizing Spateo, a temporally resolved embryonic cell atlas is achieved at key developmental time points E9.5 and E11.5.[5] During the malignant progression of tumors, there exists temporal heterogeneity in the formation of micro-areas within the same tissue slices, primarily manifested as changes in the size of representative structural micro-areas, spatial distribution of molecules, and variations in molecular abundance. By analyzing these phenomena, we can infer the reconstruct the evolution of tumor-associated micro-areas, decipher the reciprocal crosstalk between tumors and their microenvironment, and characterize metabolic reprogramming events driving tumor heterogeneity.

Spatial multi-omics technologies are in their early stages. Theoretically, the integration of multi-spatial omics data enables the construction of multi-scale spatiotemporal datasets with single (sub) cellular resolution and large field-of-view 3D/4D spatial coverage. A critical step in spatial omics data alignment involves appropriate modeling of the "spatial context". To clarify multiple spatial omics fusion, it is recommended to adopt an unsupervised, data-driven approach to achieve reliable spatial alignment and subsequent analysis for the homogeneous or heterogeneous slices. For time-series tissue slices, progressive pairwise alignment should be implemented to reconstruct multiple biological layers, thereby interpreting non-rigid structural changes and shifts between slices while adaptively correcting potential deformation artifacts. Meanwhile, through dataset enhancement and expansion, cross-modal alignment and analysis of data from the same tissue type should be conducted to leverage complementary advantages in spatial resolution and multi-omics coverage, ultimately revealing critical regulatory pathways. Alignment and analysis framework of multi-spatial omics needs to be designed as a flexible architecture, facilitating subsequent adjustments, cross-technology comparative alignment, cross-species module extensions, and continuous optimization.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.