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Voices

The impact of multi-omics in medicine

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Cracking the code of cancer through spatial multi-omics

Recent advances in spatial multi-omics and molecular imaging technologies have transformed our ability to study cancer. These platforms, combined with advanced bioinformatics, offer exceptional capabilities for profiling cancer cells and the tumor microenvironment (TME). Among their many potential applications, they show a unique advantage in investigating the spatial organization of various cell types in tissue environments and dissecting their complex interactions with neighboring cells.

A cell's phenotype and function can be significantly shaped by interactions with its neighbors. The organization and interactions of cells in the TME are not random but intricately orchestrated in ways we don't yet fully understand. Studies have identified recurrent spatial organization patterns of cells that form distinct cellular neighborhoods within the TME, creating microenvironments with unique properties that influence the fates, phenotypic states, and functions of resident cells. For instance, tumor-infiltrating T cells or cancer-associated fibroblasts across different neighborhoods within the same tumor may display markedly distinct organizational and transcriptomic features and cell interactions.

Future advancements in single-cell spatial platforms with greater gene coverage or whole-transcriptome capabilities will enable more comprehensive analyses of cancer cells and the TME. These advancements could decode cell interactions and link cell spatial organization patterns and communication circuits to their phenotypic and functional properties. With advanced machine-learning approaches, we may predict a cell's fate, phenotype, function, and response to a treatment based on these spatial features and interactions. Such advancements may facilitate the translation of spatial profiling discoveries into clinically informative insights and therapeutic strategies.

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Harnessing multi-omics to decode aging complexity

Aging is a complex process characterized by intricate and dysregulated biochemical and cellular activities, and this complexity is intensified by the cumulative effects of lifelong influences. Each omics offers specific strengths and weaknesses in exploring different aspects of aging. Advances in multi-omics approaches offer unparalleled discovery capabilities that enable comprehensive views of aging networks and capture the complex interactions and regulatory networks involved.

Spatiotemporal omics, such as spatial transcriptomics and metabolomics, now allow for the spatial exploration of aging hotspots within various organs, linking these events to specific cell types and interacting niches. Further development in multi-omics with a spatiotemporal dimension could facilitate tracking these changes across different regulatory layers and identifying key factors contributing to aging-related alterations. Notably, discrepancies across different omics layers are not rare and often lead to novel findings.

At the cohort level, techniques such as DNA methylomics or single-cell transcriptomics of blood mononuclear cells, along with plasma proteomics, have enabled the investigation into the asynchronous nature of aging and the heterogeneity among organs and individuals. The integration of in-depth multi-omics studies offers the potential to further clarify this stratification of aging heterogeneity, develop quantitative measures of age and aging rate, and construct aging clocks capable of identifying periods of accelerated aging or abrupt transitions. These advances will enhance our understanding of aging and facilitate the development of tailored aging interventions.

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The impact of multi-omics on the study of neurodegenerative diseases

The emergence of brain multi-omics has significantly transformed the investigation of neurodegenerative diseases, providing a more comprehensive understanding of the intricate molecular mechanisms underlying these conditions. Machine-learning approaches that integrate multi-omics data are helping to elucidate the underlying molecular pathways and pathogenic mechanisms involved in neurodegenerative disorders. By combining diverse omics modalities, including genetics, transcriptomics, proteomics, and metabolomics, we can now capture the complex interplay between various biological systems that contribute to the development and progression of neurodegenerative disorders and comorbidities, which might be overlooked by single-omics approaches.

Comprehensive analysis of large patient cohorts using high-throughput omics technologies has uncovered significant molecular heterogeneity and multiple dysregulated pathways associated with cognitive function and disease progression in neurodegenerative disorders. In Alzheimer's disease specifically, various lines of evidence, including our own research, support the existence of distinct molecular subtypes that parallel previously identified neuropathological and neuroimaging-based subtypes. These molecular insights are being harnessed to discover novel cerebrospinal fluid and blood-based biomarkers that could enable early detection and intervention before the disease advances to an irreversible stage. These discoveries hold promise for advancing early diagnosis, personalized treatment approaches, and drug development for neurodegenerative diseases.

As the field of multi-omics continues to evolve with advancements in spatially resolved omics at single-cell resolution and novel computational capabilities, its impact on the study of neurodegenerative diseases is poised to grow exponentially. This progress will translate into the identification of novel therapeutic targets and biomarkers for these devastating conditions.

Justin A. Boddey
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Multi-omics and medicines for malaria

Multi-omics has revolutionized how researchers functionally explore individual components of a biological system. In my field of malaria, there's perhaps no better example of the impact of functional multi-omics than in defining the modes of action and resistance of antimalarial drugs.

Chloroquine was central to malaria eradication programs of the past, but resistance developed around the world, including in Africa, where malaria exerts its most pernicious effects, having dire consequences on its medical use. Chloroquine prevents malaria parasites from effectively sequestering toxic heme during hemoglobin consumption. Functional genomics of chloroquine-resistant parasites identified polymorphisms in a membrane transporter (PfCRT) that enabled chloroquine efflux from the target organelle, where hemoglobin is digested.

Today, artemisinin is a frontline defense against malaria and has saved millions of lives across the developing world; however, its effectiveness is threatened by resistance development. Multi-omics approaches identified proteasome inhibition and damaged proteins within artemisinin-treated parasites. Polymorphisms in the parasite's Kelch 13 protein were identified in artemisinin-resistant parasites, which downregulates hemoglobin consumption. As artemisinin is a pro-drug activated during hemoglobin digestion, reduced endocytosis of this erythrocyte protein diminishes artemisinin's effect.

Artemisinin combination therapy is currently the mainstay of chemotherapy, and piperaquine is a widely used partner drug. Yet, mutations in PfCRT and amplification of *plasmepsin II/III* are drivers of piperaquine resistance. As antimalarials continue to lose their effectiveness, robust replacements with new modes of action are vital to continue the fight. The application of functional genomics to malaria remains as important as ever.

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Multi-omics and the study of the airway microbiome

My field of study is the airway microbiome and its functional roles and interactions with the human host in respiratory health and diseases. The application of multi-omics along the interface of microbe-host interaction, including metagenomics, metatranscriptomics, metabolomics, and proteomics, paired with mechanistic studies, have provided unprecedented insights into how individual airway microbes regulate host immunological processes through metabolites and peptides. Through multi-omics, insights are also gained on how environmental exposure impacts respiratory health via the microbiome. The emergence of single-cell multi-omics is providing further information on microbe-host interaction at a single-cell resolution. In addition to disease understanding, multi-omics has also demonstrated its greater power in the diagnosis, endophenotyping, and prognostication of respiratory diseases compared with traditional clinical parameters or a single type of omics data, showing its translational value in interrogating disease heterogeneity. Despite progress, challenges remain in utilizing the massive multi-omics data, in particular in integrating the high-dimensional multi-omics data in a statistically rigorous, computationally efficient, and biologically meaningful manner. It is expected that with larger disease cohorts, more advanced sequencing techniques, and innovative algorithms including artificial intelligence, multi-omics will reshape our understanding of the airway microbiome and its promise as a biomarker and a therapeutic target in the emerging era of personalized medicine.

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Gaining knowledge from the pieces of human hearts

The human heart is composed of multiple different cell types and numerous cell states that work in unison to accomplish normal tissue function. In pathological states, the cell synchrony starts to unravel, causing both local and systemic, small and sizable changes that, in time, may lead to manifestation of symptoms and a diagnosable disease. Until recently, most of these cellular and molecular changes have remained uncharacterized. With the rise of (single-cell) multi-omics, we are finally starting to see the finer details, gaining a window to the molecular function of the cardiac tissue, albeit frozen in time. With the snapshots we obtain, we are learning to trace the effects of genetic and environmental factors on genome function and to read the epigenetic code on a whole new level. We build interactive gene expression networks, combining knowledge with predictions, and allow the data to arrange themselves to form new insights into human cardiovascular biology. We gather information on small molecules secreted by the cells in various conditions and their interactions within the biological system and interpret the data in tissue contexts with spatial technologies. As the accuracy, depth, and resolution of these methods improve, more information can be extracted from less tissue, enabling new viewpoints into human cardiac function using samples originating from living patients, bringing us closer to personalized medicine and more informed translation of biological findings into clinical applications.

DECLARATION OF INTERESTS

J.A.B. is an advisory board member for *Cell Reports Medicine* and is a co-inventor on patents for the use of antimalarials.