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INTRODUCTION

Harnessing the n+1 dimensions of single-cell omics data for the prediction and prevention of human diseases

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Recent emphasis on precision medicine acknowledges the drawbacks of a one-size-fits-all approach to patient care. Advances in high-dimensional, single-cell omics technologies have enabled a parallel and synergistic movement in biomedical research that recognizes the need to capture cellular heterogeneity when deciphering the pathophysiological mechanisms of human diseases. Recent breakthroughs in spatial transcriptomics and proteomics have made yet another dimension — the n+1 dimension — accessible to the investigator to fully characterize the cellular architecture and spatial organization of human tissue in health and disease states.

However, as the dimensionality of omics datasets increases, so do barriers and challenges in processing and analyzing large-scale omics data. This analytical bottleneck has hindered the meaningful translation of high-dimensional omics datasets into diagnostic or therapeutic clinical use cases. The early days of experimental medicine that held the possibility of progressing linearly through the phases of observation to hypothesis, experiment, results, and interpretation have now morphed into a tortuous path where observation increasingly involves interrogation of gargantuan datasets collected in a comparably limited number of patient samples. Even a seemingly straight forward process like identifying cell subsets to define the single-cell feature space has become an intricate analytical feat. As pointed out by Medina et al. in this special issue, this problem is compounded in many disease states, such as cancer, where cells aberrantly express markers that are typically utilized for cell phenotyping [1].

This issue further explores how single-cell technologies, particularly those that afford spatial resolution, are currently implemented in clinical outcome studies for the discovery of predictive biomarkers, novel pathobiological mechanisms, or therapeutic targets. Drawing from examples across multiple technologies, such as single-cell RNA sequencing (scRNAseq), spatial transcriptomics, COdetection by indexing (CODEX), and suspension and imaging mass cytometry (IMC), and diseases (from infectious and neurovascular diseases to transplantation and cancer), all authors contributing to this special issue emphasize important considerations with respect to clinical study design, sample processing, and the choice of machine learning-based analytical pipelines [1–10].

Several articles of this special issue focus on application of spatial proteomics and transcriptomics technologies to study the tumor immune microenvironment. In their review, Glasson et al. shed light on how spatial omics can be leveraged to characterize dynamically the cellular ecosystem of solid tumors over time and over the course of treatment [2]. Wlosik et al. discuss future prospect for high-content suspension and tissue-based omics approaches to address the need for predictive biomarkers of non-small cell lung cancer (NSCLC) clinical outcomes [3]. As the authors point out, existing NSCLC biomarkers are already employed to assign patients to treatment despite being inaccurate predictors of patient clinical outcomes. Similarly, Funingana et al. discuss the challenges of conventional chemotherapy resistance and non-response to immunotherapy in treating ovarian tumors [4], while Lo et al. emphasize the critical need for predictive biomarkers of treatment response and new therapeutic targets in the context of pediatric oncology [5]. In each clinical use-case, the potential of high-dimensional single-cell analysis of the tumor microenvironment combined with other omics modalities, such as genomics and radiomics,

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for improving cancer screening and surveillance of individualized therapeutic treatment is emphasized.

An additional topic covered by several within this special issue focuses on clinical scenarios where application of single-cell omics technologies is less mature than in cancer research, or just emerging. Ratnasiri et al. summarize recent advances in scRNAseq approaches to identify novel mechanisms of host–pathogen interactions for the much-needed development of new antiviral therapeutics [6]. Barbetta et al. discuss the latest application of high-plex imaging techniques, particularly IMC, to identify predictive biomarkers of solid organ transplant rejection [7]. In this clinical context, the authors highlight how identification of patient- and organ-specific immune signatures of transplant tolerance may allow patients to reduce their reliance on immunosuppression and facilitate the discovery of new therapeutics for the prevention of graft rejection. Technological and analytical advances in IMC and suspension mass cytometry are also a core focus of Einhaus et al.'s review of systemic and local immune responses in patients with oral mucosal pathologies, a poorly understood group of diseases comprising not only aggressive malignancies but also severe auto-immune disorders [8]. Finally, Maïer et al. examine recent applications of single-cell technologies and multiplex imaging to characterize thrombo-inflammatory events in patients suffering from acute stroke and to derive multi-omics predictive models for the development of hemorrhagic transformation, a devastating complication after revascularization therapy [9].

In all these reviews, a recurring theme is the need for standardization of sample collection and processing, and for rigorous and reproducible computational pipelines for the analysis of the high-dimensional omics data. For example, Einhaus et al. delineate the sequential steps of IMC analysis from sample pre-processing to cell segmentation, marker identification, and systematic extraction of spatial features, a complex process currently at the discretion of the researcher to choose from diverse techniques, software, and analysis pipelines [8]. The same is true for the CODEX multiplex imaging platform, which requires continued fine-tuning of staining protocols, manual or automated cell identification strategies, feature extraction, and data analysis methods detailed in Kuswanto et al. [10]. Importantly, for every biological specimen analyzed, a heterogeneous dataset is generated that can be subdivided into multiple data layers of varied dimensions and information-content, such as phenotypic, functional, and cell-neighborhood data layers. As such, the choice of a statistical framework adapted to the multi-omics integration of individual data layers is paramount for rigorous modeling of the high-dimensional data and identification of robust and clinically relevant biological features associated with the clinical endpoint of interest. On this subject, several reviews (e.g., 1, 5, 8, 9) elucidate recent advances towards a unified statistical framework for analysis of high-dimensional omics data, including recent sparsity-inducing machine learning algorithms that allow effective data integration while maintaining predictive performance.

The translation of single-cell technologies and spatial omics into precision medicine assays is undoubtedly a new frontier in biological sciences. Occasionally, the field resembles the wild west of biomedical research as scientists have access to an unprecedented array of technologies, workflows, and analytical pipelines with few standardized guidelines. Despite these challenges, implementation of these powerful technologies in clinical studies is exciting and offers tangible promises for identification of robust predictive biomarkers of currently unpredictable clinical outcomes and development of novel therapeutic interventions for previously incurable diseases.

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