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EDITORIAL

Intratumoral heterogeneity: Targeting origin vs. variations and AI-driven non-invasive assessment

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Clonal growth in cancers leads to intra-tumor heterogeneity (ITH), thereby complicating diagnosis and treatment. The TRACERx lung cancer study highlighted the intricate relationship between intratumoral heterogeneity and clinical outcomes, demonstrating that genetic alterations such as whole-genome doubling and subclonal expansions influence tumor proliferation and patient survival. In addition to genetic alterations, epigenetic modifications significantly impact tumor complexity and drug resistance. Multi-omics approaches are anticipated to be crucial for accurately characterizing ITH. As ITH becomes increasingly complex, therapeutic challenges are anticipated to escalate. Early intervention targeting the causes of genetic instability may enhance outcomes in tumor therapy. Future evaluations of ITH in advanced tumor stages will require non-invasive methodologies. A potential solution for this demand involves integrating artificial intelligence (AI) technologies with imaging or pathology data to predict significant tumor characteristics. Further research is necessary to assess the capability of AI methods, in conjunction with multi-omics data, to accurately predict ITH characteristics relevant to

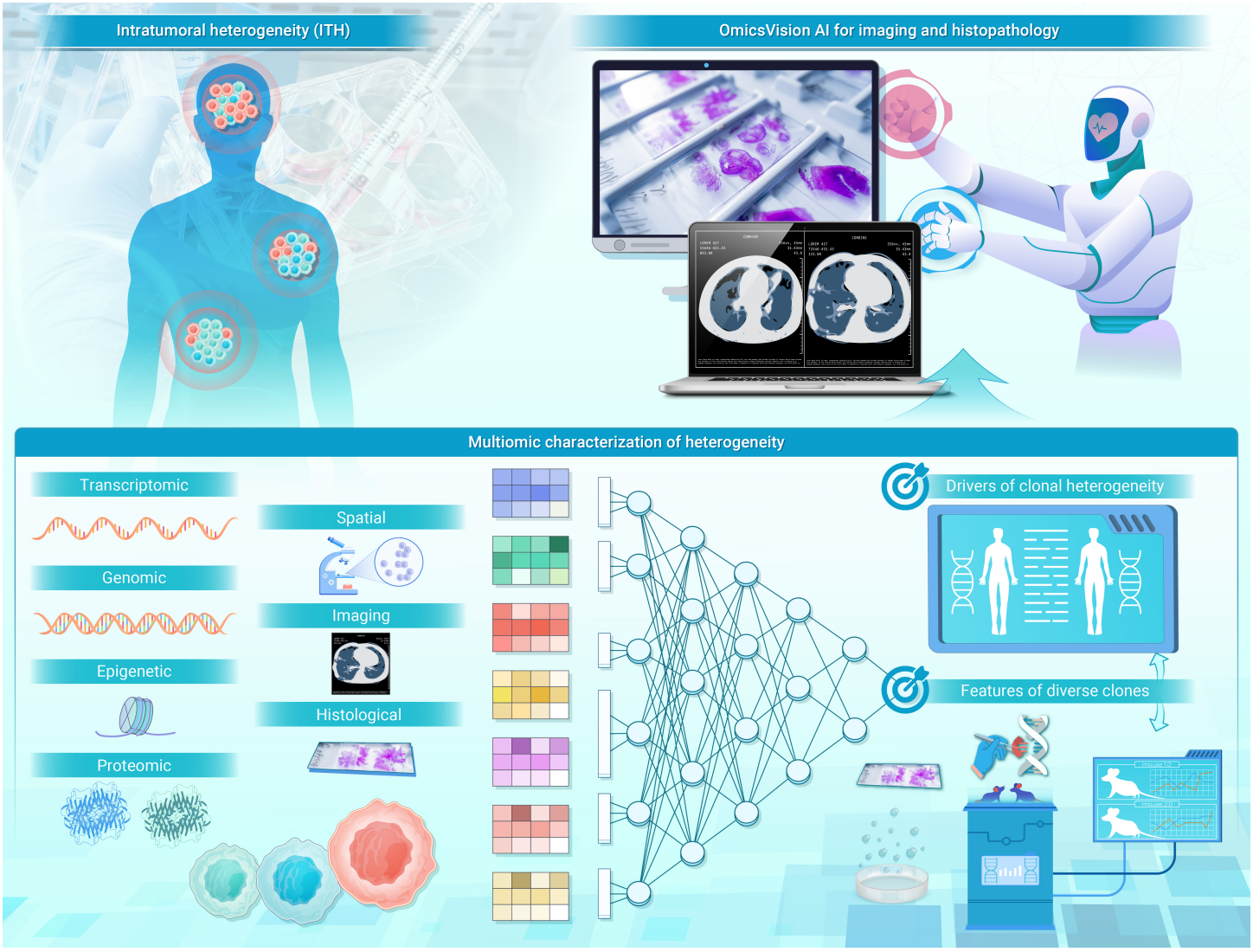

Figure 1. Multi-omics profiling of tumor heterogeneity and AI-based non-invasive evaluation This graphic maps intratumoral heterogeneity (ITH) by combining spatially resolved multi-omics profiling—including transcriptomic, genomic, epigenetic, proteomic, and histopathological studies—into using deep learning methods to decipher spatially diverse omic patterns and forecast clonal dynamics, an artificial intelligence (AI) framework analyzes multimodal data from radiological imaging (e.g., MRI/CT) and digitalized histopathology slides. Symbolic of the robotic figure, the AI system independently generates useful insights that allow non-invasive assessment of tumor progression and therapeutic vulnerabilities.

tumor treatment, prognosis, and pharmaceutical response.

EVOLUTIONARY DYNAMICS, MULTI-OMICS PROFILING, AND THERAPEUTIC PARADIGMS

Cells may transform into tumor cells due to the continuous accumulation of genetic alterations influenced by driving events. ITH results from heightened genomic instability, which propels clonal evolution and fosters mutational occurrences. ITH complicates the treatment and diagnosis of malignancies. Recent TRACERx lung cancer research findings provide significant new insights into the relationship between ITH and clinical outcomes[1]. Disease-free survival may be influenced by whole-genome doubling (WGD) in subclones, with some subclonal expansions potentially impacting patient survival. Additionally, intratumor copy number variability is associated with recurrence risk.

Nonetheless, DNA mutations or chromosomal changes alone cannot sufficiently characterize ITH. Epigenetic alterations, such as DNA methylation, histone modifications, RNA expression, and protein modifications, significantly influence cellular phenotype. Furthermore, intricate interactions within the tumor microenvironment influence the formation of the tumor cell population. Future research must integrate genomes, transcriptomics, epigenomics, proteomics, and metabolomics to enhance our understanding of ITH and clone-specific characteristics. Multi-omics methodologies will enhance our understanding of the molecular mechanisms behind tumor proliferation, facilitating the identification of novel treatment targets, despite potential challenges in data integration.

Combination therapies targeting many tumor clones or various processes inside carcinogenesis may become increasingly complex. These treatments, however, can merely decelerate tumor growth temporarily without yielding a cure. Focusing on the initial stages of tumor evolution rather than adjusting treatment strategies based on the tumor's dynamic alterations may present a more compelling approach. This strategy aims to preempt the emergence of resistant clones and significant genetic variation. Early intervention provides a more enduring treatment by potentially altering the tumor's evolutionary trajectory. This strategy may help mitigate the enduring issue of treatment resistance by preventing the first formation of tumor heterogeneity.

GENOMIC INSTABILITY AND THERAPEUTIC RESISTANCE: TARGETING EARLY EVOLUTIONARY DRIVERS TO OVERCOME ITH

A primary challenge in addressing ITH, genomic instability, is essential for cancer progression. Recent findings from the TRACERx lung cancer study indicate that WGD and TP53 co-mutations enhance genomic instability, leading to copy number aberrations that augment resistance to EGFR-targeted therapies[2]. A significant factor influencing ITH and chromosomal instability is the loss of FAT1, which undermines homologous recombination repair[3]. These findings illustrate the interplay between treatment resistance, heterogeneity, and genetic instability. The dynamic nature of tumor genomes presents significant challenges for cancer therapy.

Efforts have been undertaken to mitigate the consequences of genomic instability by targeting its downstream effects, hence reducing treatment resistance[4]. The efficacy of early intervention, which addresses the root cause of instability, remains a subject of contention. In the initial phases of cancer progression, genome stabilization may inhibit the proliferation of novel drug-resistant clones. This may further reduce the tumor's ability to mutate and acquire therapy resistance. Stabilizing a genome undoubtedly requires a synthesis of immune system therapies, epigenetic modifications, and alterations to DNA repair mechanisms. Nevertheless, a more precise definition of "early" necessitates additional cohorts to investigate variations among different cancers.

AI-DRIVEN PRECISION IN ONCOLOGY: MULTIMODAL INTEGRATION OF IMAGING, PATHOLOGY, AND OMICS FOR NON-INVASIVE ITH PROFILING AND THERAPEUTIC INNOVATION

When surgical interventions are no longer viable, especially in cases of extensive metastasis, pharmacological treatment for tumors typically becomes necessary. Thus, guiding healthcare decisions relies on non-invasive assessment methods. While multi-omics methodologies can precisely delineate the molecular attributes of a tumor, they require validation through comprehensive cohort studies and substantial financial commitment before achieving therapeutic affordability. While liquid biopsy technology represents a burgeoning and highly promising method for the noninvasive evaluation of tumor cell features, the routine utilization of imaging and pathology slides to detect ITH in clinical settings does not necessitate further sample collection. Direct application of these approaches to predict multi-omics traits may demonstrate greater cost-effectiveness in clinical settings. Advancements in AI technology enable more accurate data interpretation by facilitating the integration of multi-omics results with imaging or histology features[5].

The domain has evolved from an initial dependence on convolutional neural networks (CNNs) to more sophisticated methodologies, including transformers and foundation models. AI research is currently concentrating on more complex applications, such as predicting patient outcomes and assessing treatment efficacy, rather than basic tasks like sorting, recognizing, and categorizing images. AI-driven image analysis is utilized in pathology to identify potential immune cell biomarkers in tumors, such as cytotoxic T cells, PD-L1 expression, tumor-infiltrating lymphocyte density, and the spatial relationships of immune cells within the tumor microenvironment. Concurrently, AI analytical approaches have evolved from models that have progressed beyond weakly supervised learning to self-supervised learning, facilitating the acquisition of knowledge from extensive amounts of unlabeled data. This minimizes the demand for detailed hand labeling and supports additional research and development initiatives.

AI technologies have showed considerable promise in analyzing ITH. Notwithstanding commendable outcomes in many research, the precision of AI technology in evaluating ITH fluctuates. Accuracy rates frequently over 85% have been documented in the classification of tumor subtypes and the identification of regions with significant heterogeneity. CNN-based models have demonstrated AUC values over 0.9 in glioma studies for predicting ITH. Nonetheless, the sensitivity and specificity of AI models in clinical practice often vary between 70-90%, and model efficacy may differ based on the quality and origin of the data. AI has exhibited the capability to identify elements in photographs that elude human perception. Nevertheless, histological abnormalities associated with ITH exhibit characteristics that require a substantial collection of pictures for analysis and investigation. These variables encompass clonal makeup, mutation spectrum characteristics, immune microenvironment composition, and their precision in assessing efficacy, prognosis, and medication response.

We anticipate that it provides a superior, non-invasive method for assessing ITH or characterizing tumor clones, hence enhancing convenience and affordability in clinical decision-making. Multimodal AI is rapidly increasing, integrating data from various sources such as pathology slides, radiographic images, genetic information, and clinical reports. This integration significantly enhances the predictive capability of AI and its potential to improve therapeutic decisions. Further research is necessary to ascertain whether the integration of radiographic and pathology data produces enhanced outcomes, as it may introduce extra complexities for clinical applications and regulatory approval. These advancements enable scientists to extract biomarkers or biological attributes from biobanks, in conjunction with imaging characteristics, to enhance diagnostic and treatment decision-making, as well as to conduct more effective retrospective investigations. AI optimizes and automates potential clinical trials, thereby improving the efficiency and cost-effectiveness of drug development. While there are currently few forthcoming clinical research utilizing AI, this approach holds significant potential for the future.

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DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.