Dong *et al. Cancer Cell International* (2025) 25:317
https://doi.org/10.1186/s12935-025-03944-2

Cancer Cell International

REVIEW Open Access

Integration of multi-omics approaches in exploring intra-tumoral heterogeneity

Mengmeng Dong[1,2†], Liping Wang[1,2†], Ning Hu[1], Yueli Rao[4*], Zhen Wang[2*] and Yu Zhang[3*]

Abstract

Intra-tumoral heterogeneity (ITH) is common in malignant tumors and arises from dynamic variations across genetic, epigenetic, transcriptomic, proteomic, metabolic, and microenvironmental factors. This complexity drives tumor evolution and treatment resistance, undermining the accuracy of clinical diagnosis, prognosis, and treatment planning. Despite recent advances in multi-omics technologies that enable comprehensive mapping of ITH across molecular layers, major challenges remain in clinical translation. This review outlines the principles and clinical applications of eight major omics modalities in the context of ITH: genomics, single-cell genomics, transcriptomics, epigenomics, proteomics, radiomics, microbiome, and metabolomics. We highlight the unique contributions of each omics platform to tumor profiling and emphasize how their integration enhances biological interpretation, patient stratification, and biomarker discovery. Furthermore, we will focus more extensively on the limitations of applying these approaches to ITH analysis. Instead of providing an exhaustive catalog, this review highlights major controversies, technical hurdles, and conceptual gaps that impede the clinical translation of multi-omics-based ITH analysis, with the aim of addressing ITH-related clinical challenges.

Keywords Intra-tumoral heterogeneity, Multi-omics, Cancer evolution, Tumor plasticity, Biomarker discovery

Introduction

Despite extensive research over decades, cancer continues to be a leading global cause of mortality, largely due to the complex and poorly understood interactions among genetic, epigenetic, environmental, and immune factors. Among these challenges, intra-tumoral heterogeneity (ITH) represents a particularly formidable barrier, characterized by the coexistence of genetically and phenotypically diverse subclones within a single tumor. ITH challenges the core assumption of targeted therapy—that a single molecular signature can guide treatment—and directly contributes to drug resistance, disease relapse, and diagnostic uncertainty. Conventional bulk tissue analysis often overlooks the subtle cellular heterogeneity within tumors, resulting in incomplete or misleading interpretations of tumor biology.

While multi-omics technologies hold promise for unraveling the cellular complexity of cancer, their clinical

†Mengmeng Dong and Liping Wang contributed equally to this work.

*Correspondence:
Yueli Rao
raoyueli@sohu.com
Zhen Wang
wangzhen@hmc.edu.cn
Yu Zhang
1013950738@qq.com
[1]Department of Chemistry, Zhejiang University, Hangzhou 310058, China
[2]Center for Laboratory Medicine, Allergy Center, Department of Transfusion Medicine, Zhejiang Provincial People's Hospital People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou 310014, China
[3]Department of Gastroenterology, Zhejiang Provincial People's Hospital, Hangzhou Medical College, Hangzhou 310014, China
[4]Department of transfudioD Medicine, Joint Service Support Force 903 Hospital, Hangzhou 310014, China

implementation remains limited by challenges in data interpretability, high dimensionality, and integration bias. Each omics layer offers a distinct but partial view. For instance, genomics identifies clonal architecture, transcriptomics and epigenomics reflect regulatory programs, and proteomics captures downstream effectors. Yet none alone provides a comprehensive picture. Only by integrating these orthogonal layers can we move from partial observations to systems-level understanding of ITH. In contrast, multi-omics integration facilitates cross-validation of biological signals, identification of functional dependencies, and the construction of holistic tumor "state maps" linking molecular variation to phenotypic behavior. This approach improves tumor classification, resolves conflicting biomarker data, and enhances the predictive power of treatment response models. Importantly, integrative frameworks can uncover latent resistance drivers or subclonal architectures that remain undetectable in single-layer datasets. However, challenges including data harmonization, model interpretability, and cumulative noise across modalities remain major barriers to clinical translation, necessitating rigorous methodological innovation and conceptual clarity in future research.

This review critically evaluates the use of multi-omics strategies in characterizing ITH, highlighting both notable advances and persistent limitations. Our focus extends beyond technical innovations to unresolved issues such as integrating conflicting data layers, modeling dynamic heterogeneity, and mitigating spatial sampling bias. Ultimately, this review aims to illustrate how integrated omics strategies enhance our understanding of tumor heterogeneity, paving the way toward more effective and personalized cancer therapies.

Literature selection strategy

This narrative critical review aims not to exhaustively list all studies, but to select and critically evaluate the most influential, representative, and conceptually insightful literature on ITH and multi-omics integration. A structured literature search was performed in PubMed, Web of Science, and Scopus databases, covering January 2020 to May 2025. Keywords and their Boolean combinations included: "tumor heterogeneity," "intra-tumoral heterogeneity," "multi-omics," "genomics," "single-cell," "transcriptomics," "proteomics," "epigenomics," "radiomics," "metabolomics," "microbiome," and "precision oncology." Relevant Medical Subject Headings (MeSH) terms were added when applicable to expand the search scope. Inclusion criteria included: (i) peer-reviewed original research, reviews, or meta-analyses published in English; (ii) studies on human cancers or translationally relevant in vivo/in vitro models; and (iii) research providing mechanistic insights or conceptual frameworks related to ITH and/or multi-omics analysis. Exclusion criteria were: (i) conference abstracts, preprints without peer review, or non-English studies; (ii) studies limited to single-omics without relevance to ITH; and (iii) articles lacking methodological clarity or translational relevance. Two authors independently performed literature selection and quality appraisal. Studies were evaluated according to methodological rigor, citation impact, clinical relevance, and alignment with the review's objectives. Final inclusion was determined by consensus to ensure comprehensive coverage and critical depth, facilitating identification of agreed findings, unresolved controversies, and emerging directions.

Cancer statistics and intra-tumoral heterogeneity

The American Cancer Society annually reports nationwide estimates of cancer incidence and mortality in the United States. In 2024, an estimated 2,001,140 new cancer cases and 611,720 cancer-related deaths are an estimated [88]. The COVID-19 pandemic significantly disrupted early cancer screening and treatment, leading to diagnostic delays and interruptions in care. However, public health systems adapted over time, mitigating these disruptions [67]. Among newly diagnosed cancers, the most common types are those of the genital system (427,800 cases), digestive system (353,820 cases), and breast (313,510 cases). Regarding cancer-related deaths, the highest numbers are anticipated for cancers of the oral cavity and pharynx (174,320 deaths), tongue (130,450 deaths), and mouth (125,070 deaths) [88]. Detailed statistics are shown in Fig. 1. Cancer prevalence is slightly higher in men (40.5%) than in women (38.9%), likely due to complex interactions among sex hormones, immune responses, and lifestyle-related risk factors [39]. Lung cancer remains the leading cause of cancer-related mortality worldwide. Well-established risk factors, such as tobacco use, alcohol consumption, high-fat diets, and certain sexual behaviors, are strongly associated with multiple cancer types [113]. A major clinical challenge in oncology is that many early-stage cancers are asymptomatic, often leading to delayed diagnosis. As a result, tumors frequently progress to advanced or metastatic stages before detection, limiting curative treatment options and reducing therapeutic benefits [96]. Although current treatment approaches, such as surgery, chemotherapy, radiotherapy, and molecular targeted therapy, can reduce tumor burden and extend survival, their effectiveness is often compromised by cancer cell plasticity and adaptability. This limitation largely stems from ITH, defined as the coexistence of genetically, epigenetically, and phenotypically distinct subpopulations within a single tumor [8]. ITH enables tumor cells to evade treatment, metastasize, and develop resistance. Therefore, a comprehensive understanding ITH is essential

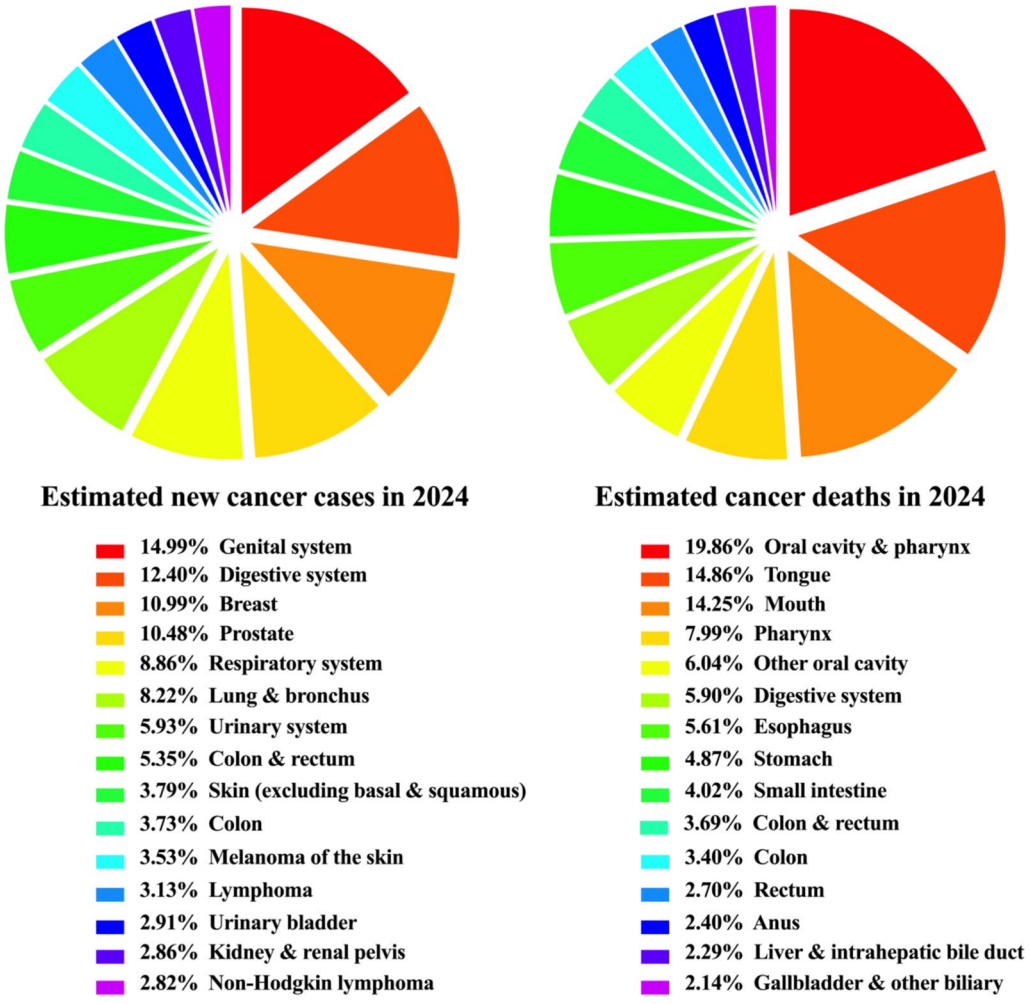

Fig. 1 Estimated cancer incidence and mortality by system and gender in the United States (2024). Data based on [88]

for developing more effective and durable therapies that target the mechanisms underlying cancer persistence and progression.

The concept of ITH was first introduced by German physiologist Johannes Müller. ITH encompasses both inter-regional and intra-clonal variations, which critically influence tumor initiation, progression, and therapeutic response. Due to its profound impact on cancer diagnosis, prognosis, and treatment efficacy, ITH represents a major challenge in precision oncology. Therefore, a thorough understanding of ITH is essential for optimizing cancer prevention, early detection, treatment selection, and outcome prediction. ITH arises from both genetic factors (e.g., somatic mutations and copy number alterations) and non-genetic factors, including epigenetic modifications, proteomic plasticity, metabolic reprogramming, and alterations in the TME. Together, these factors drive tumor aggressiveness and contribute to therapeutic resistance [9]. As tumors evolve, ITH progresses through adaptive selection and clonal expansion, often leading to treatment failure and relapse. Therefore, therapeutic strategies that target both intrinsic tumor features and microenvironmental interactions offer the potential for synergistic effects and improved clinical outcomes. However, conventional preclinical models typically fail to fully capture the complexity of human ITH, highlighting the need for clinical trials to validate novel interventions.

Recent advances in next-generation sequencing (NGS) and multi-omics technologies have enabled high-resolution quantification and characterization of ITH. This review focuses on the integration of large-scale multi-omics datasets with computational algorithms to assess ITH in clinical cancer cohorts. We also highlight emerging clinical studies that apply multi-omics approaches for patient stratification and longitudinal disease monitoring (Fig. 2). To emphasize the clinical relevance, we prioritized studies with prospective clinical data and well-defined patient cohorts when compiling Table 1. Table 1 summarizes recent applications of omics data in clinical

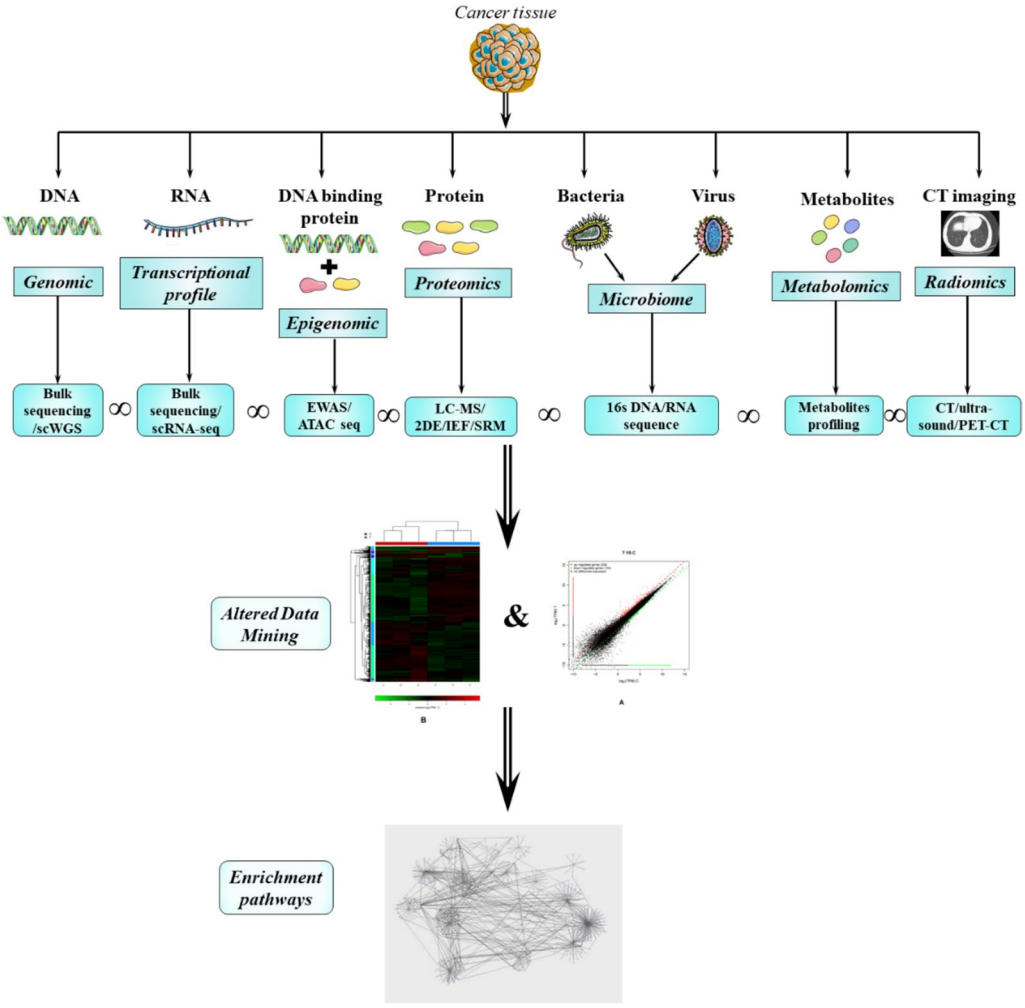

Fig. 2 Applications of Omics in Cancer

trials addressing ITH, offering valuable insights for biomarker development and future research directions.

This figure illustrates the applications of omics technologies in cancer research. Currently, multiple omics methods are often combined to achieve synergistic insights into cancer biology. Integrated analyses of multi-omics data have highlighted significant alterations in several major pathways, revealing therapeutic heterogeneity across different cancers. Moreover, differential molecular signatures between tumor samples and healthy controls can serve as biomarkers for monitoring cancer development and progression.

Multi-omics approaches in addressing intratumoral heterogeneity

This section outlines key omics technologies and their individual and integrated roles in characterizing ITH. For each omics modality, we review core principles, recent methodological advances, and representative studies. We further discuss how findings from these approaches inform clinical applications. While each omics platform offers distinct advantages, their integration provides a more comprehensive understanding of tumor biology and evolutionary dynamics.

Genomics and bulk tumor sequencing

Genomic sequencing represents a foundational method for characterizing ITH. The most commonly employed techniques, whole-exome sequencing (WES) and whole-genome sequencing (WGS), offer critical insights into tumor mutational landscapes, clonal architectures, and evolutionary dynamics. These bulk sequencing techniques analyze DNA extracted from mixed populations of tumor and stromal cells, delivering a population-level overview of genetic alterations [70]. Although bulk sequencing lacks single-cell resolution, it remains invaluable for reconstructing tumor phylogenies and identifying driver mutations. For example, the TRACERx Renal study employed multi-region exome sequencing across numerous clear cell renal cell carcinoma (ccRCC)

Table 1 Clinical trials and multiple omics

Cancer types	Samples	Related Omics	Analyzed data	Approval number	References
Single cell sequencing					
Breast cancer	Biopsy of patient-derived breast xenografts: SA1135	DLP^{+} method for scWES	Detecting driver mutations *MCL1*, *MYC*, and *CCNE*, and secondary mutations *RAD18* and *RAB18;*	–	[50]
Lymphoma	21 patients	NGS	A combination of intratumoral CpG, low-dose radiotherapy, and systemic ibrutinib induces robust systemic antitumor immune responses	NCT02927964	[87]
Pancreatic adenocarcinoma	27 total patients	Large-scale chromosomal CNVs	CXCL12-CXCR4, specific to iCAFs and TAMs respectively, to be the most significant potential interaction	–	[98]
Transcriptional sequencing					
CRC	Blood samples and tissue samples from 18 patients	ScRNA-seq	Tumor-associated macrophages (TAMs) and dendritic cells (DCs) are vital regulators for cell-microenvironment interactions;	PRJEB34105	[108]
Prostate cancer	26 models from the LuCaP PDX series of advanced prostate cancer with well-defined phenotypes	WGS	The regulation of key factors such as AR, HOXB13, NKX-3.1, FOXA1, and REST has been shown from ctDNA in CRPC	PRJNA900550	[28]
Epigenomics					
AML	Human AML cell lines	ScRNA-seq, DNA barcode, ATAC-seq	Inhibition Lsd1 promotes Pu.1 links to cofactor Irf8, induces enhancer (H3K4me1/2 and H3K27ac) expressions and stabilizes epigenetic resistance;	NCT01943851	[4]
MPALs	Bone marrow from 25 patients	CITE-seq, ATAC seq	91,601 putative peak-to-gene linkage, like *RUNX1* mutation is upregulated in most subpopulations, *RUNX1* as transcriptional factor (TF) regulates CD69;	–	[37]
Radiomics					
Glioma	The different cohorts and clinicopathological characteristics of enrolled patients (N = 379)	CT for radiomics, RNA-seq	Verifies 8 features for gene expression of CD8 cells, which could identify inflammatory and immune-desert cancers;	NCT01567202	[17]
Breast cancer	Surgical specimen from 31 women patients	RNA-seq, ultrasound for radiomics	Nonparallel direction relates to increased *TEF1*, *TEF3*, *AREG*, *ARG3*, vascular structure relates to enhanced *FZD8*, reduced *IGF1R*, and reduced *CRIPAK;*	–	[77]

Studies were selected primarily based on clinical relevance, especially those involving prospective trials and longitudinal cohorts. Preclinical studies were included only when they provided critical mechanistic insights

samples, uncovering spatially distinct subclones with unique mutational signatures. Early PBRM1 mutations were linked to less aggressive tumor evolution, while late-arising subclonal mutations were associated with poor prognosis and metastatic potential [20, 59]. Similarly, in chronic lymphocytic leukemia (CLL), longitudinal bulk sequencing revealed clonal expansions harboring TP53 and NOTCH1 mutations, reflecting branched evolution and the emergence of drug-resistant subpopulations. These studies demonstrate that integrating variant allele frequencies (VAF), tumor purity estimates, and copy number variations allows for accurate inference of cancer cell fractions (CCFs)—a quantitative measure of ITH [30]. High subclonal diversity, as indicated by CCF metrics, has been associated with early relapse and resistance to targeted therapies [18]. Despite its limitations in single-cell resolution, bulk tumor sequencing continues to offer significant value in clonal reconstruction, biomarker discovery, and informing clinical decisions within the framework of precision oncology (Fig. 3).

Single-cell genomics: dissecting ITH at cellular resolution

While bulk-based sequencing approaches-such as proteomics and transcriptomics—can be adapted for single-cell resolution, they often yield averaged signals across cell populations or reflect downstream functional outputs. In contrast, single-cell genomic sequencing captures cell-to-cell genetic variability directly, offering the most refined resolution for studying ITH. As such, the single-cell layer of resolution provides the most precise lens through which the clonal complexity, lineage dynamics, and evolutionary trajectories of tumors can be observed [48]. Single-cell DNA sequencing (scDNA-seq) and single-cell whole-genome sequencing (scWGS) have revealed the genetic architecture of tumors at unprecedented resolution. In a seminal study, Navin et al. [71]

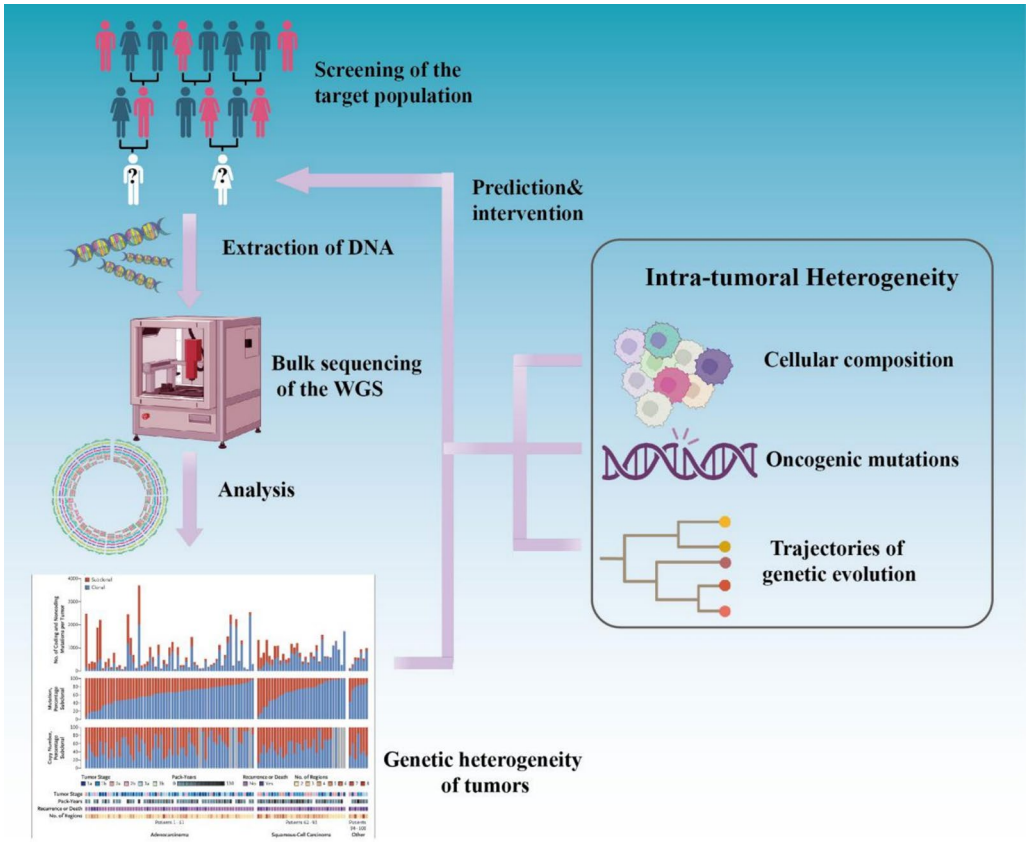

Fig. 3 WGS uncovers ITH. The sequencing was initially conducted on the target population, revealing genetic variations contributing to tumorigenesis. These findings provide critical insights for guiding timely clinical interventions and personalized treatments for at-risk populations

introduced the concept of punctuated clonal evolution in breast cancer, demonstrating the abrupt emergence of genetically distinct clones, thereby challenging traditional linear models of tumor progression [53, 83]. Further technological advances, such as Direct Library Preparation Plus (DLP+), have enabled high-throughput single-cell copy number profiling. For example, Laks et al. [50] applied DLP+ to breast cancer biopsies, identifying distinct ancestral and subclonal lineages characterized by alterations in genes such as MCL1, RAD18, and MYC. Notably, some clones exhibit loss of heterozygosity in BRCA2, correlating with germline predisposition and therapeutic vulnerabilities [50]. Beyond mutation detection, single-cell genomics is increasingly employed to explore intratumoral diversity associated with therapeutic responses. Studies in glioblastoma and lung cancer have identified drug-resistant subclones characterized by unique mutational profiles or chromosomal instability under selective pressure, insights critical for anticipating resistance and designing rational combination therapies. Emerging strategies now integrate lineage tracing with multimodal single-cell profiling, combining genomic data with transcriptomic or epigenomic data. These integrative approaches elucidate the functional consequences of genetic heterogeneity and reveal how clonal diversity contributes to tumor plasticity, immune evasion, and progression [97, 110]. Despite ongoing challenges, including technical noise, high costs, and limited scalability, single-cell genomics remains an indispensable tool in cancer research. By resolving tumors at cellular resolution, it provides a robust framework for monitoring tumor evolution, predicting therapeutic resistance, and informing precision oncology (Fig. 4).

Transcriptomics: mapping cellular diversity in tumors

Transcriptomics provides a powerful framework for investigating gene expression dynamics and cellular diversity within tumors. By capturing mRNA profiles, transcriptomic analyses reveal cellular states, differentiation trajectories, and functional programs underlying ITH. Single-cell RNA sequencing (scRNA-seq), in particular, has revolutionized our understanding of tumor ecosystems by enabling cell-specific expression profiling at large scale. For instance, Tirosh et al. [92] applied scRNA-seq to human oligodendrogliomas, identifying two distinct tumor lineages: one characterized by high expression of OLIG1, OLIG2, and OMG (oligodendrocyte precursor-like), and another expressing SOX9,

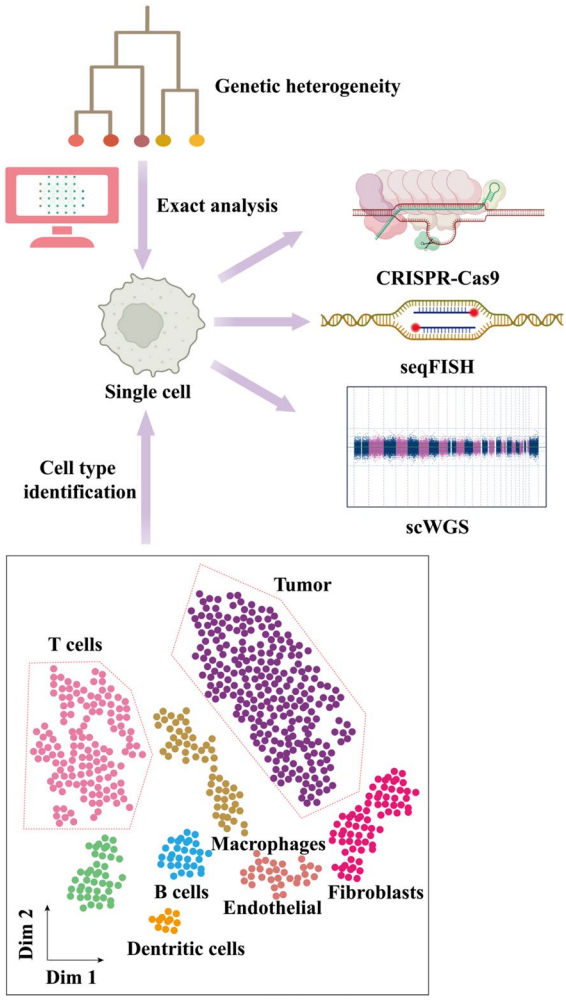

Fig. 4 The use of single-cell sequencing enables the precise analysis of the genetic landscape and uncovers the genetic heterogeneity of tumors

APOE, and ALDOC (astrocytic lineage-like). These distinct transcriptional programs suggested simultaneous differentiation pathways within a single tumor, reflecting both plasticity and developmental mimicry. In melanoma, scRNA-seq revealed rare subpopulations with stress-response signatures (FOS, JUN, NFKBIZ, ATF3) associated with resistance to RAF/MEK inhibitors. These findings are validated by in situ hybridization and functional assays, providing mechanistic insights into drug tolerance and phenotypic switching. Transcriptomics has also illuminated non-genetic mechanisms of therapeutic resistance. Bell et al. [4] demonstrated in acute myeloid leukemia (AML) that transcriptional reprogramming, rather than mutations, drove resistance to BET inhibitors. The transcription factor PU.1, stabilized by IRF8, orchestrated enhancer remodeling, redirecting BRD4 binding and establishing alternative gene expression programs in resistant clones [4]. Advances in RNA velocity, pseudotime analysis, and multimodal data integration now facilitate the inference of dynamic expression trajectories, cellular transitions, and lineage commitment. These methods reveal how transcriptional plasticity mediates adaptation under therapeutic pressure [107]. Despite challenges including technical noise, high cost, and biases due to cell dissociation, its ability to resolve cellular heterogeneity and microenvironmental interactions makes it critical for understanding tumor evolution. Overall, transcriptomics, particularly single-cell approaches, significantly contributes to identifying transcriptional states associated with resistance, relapse, and potential therapeutic targets.

Epigenomics: uncovering the regulatory landscape of tumor heterogeneity

Epigenomics investigates heritable changes in gene expression that occur independently of alterations in the DNA sequence. These mechanisms include DNA methylation, histone modifications, chromatin accessibility, and non-coding RNA regulation. Epigenetic mechanisms critically define cellular identity and plasticity, thus playing key roles in tumor progression and non-genetic aspects of ITH. Epigenetic profiles dynamically reshape transcriptional landscapes in response to environmental or therapeutic pressures [27] (Fig. 5). Aberrant DNA methylation is a hallmark of cancer, where global hypomethylation contributes to genomic instability and oncogene activation, while promoter hypermethylation silences tumor suppressors. Flavahan et al. [33] demonstrated that methylation-induced disruption of CTCF insulator elements alters chromatin architecture, facilitating oncogene activation across various cancers [33]. Furthermore, epigenetic inheritance can be compromised by epimutations caused by altered epigenetic modifiers, changes in DNA methylation, or inhibited cellular differentiation [15, 70]. For example, evolutionary analyses of Cryptococcus neoformans suggest the epigenome is maintained via Darwinian selection despite the loss of certain DNA methyltransferase genes [40]. Epigenome-wide association studies (EWAS), inspired by genome-wide association studies (GWAS), systematically correlate DNA methylation patterns with phenotypic traits, overcoming tissue heterogeneity and minimizing false-positive results [23, 79]. GWAS focuses on relative allele frequencies and copy number alterations (CNAs) of DNA variants of interested phenotypes and counterparts [85]. EWAS system manages to eraser heterogeneous differences caused by tissue sampling via alterations of DNA methylation across abundant loci and avoids false-positive results as far as possible [74, 95, 106]. Parallel with droplet-based cellular indexing of transcriptomic and epitopes by sequencing (CITE-seq), assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) integrates an intact landscape of chromatin-accessibility and transcriptomic to infer the

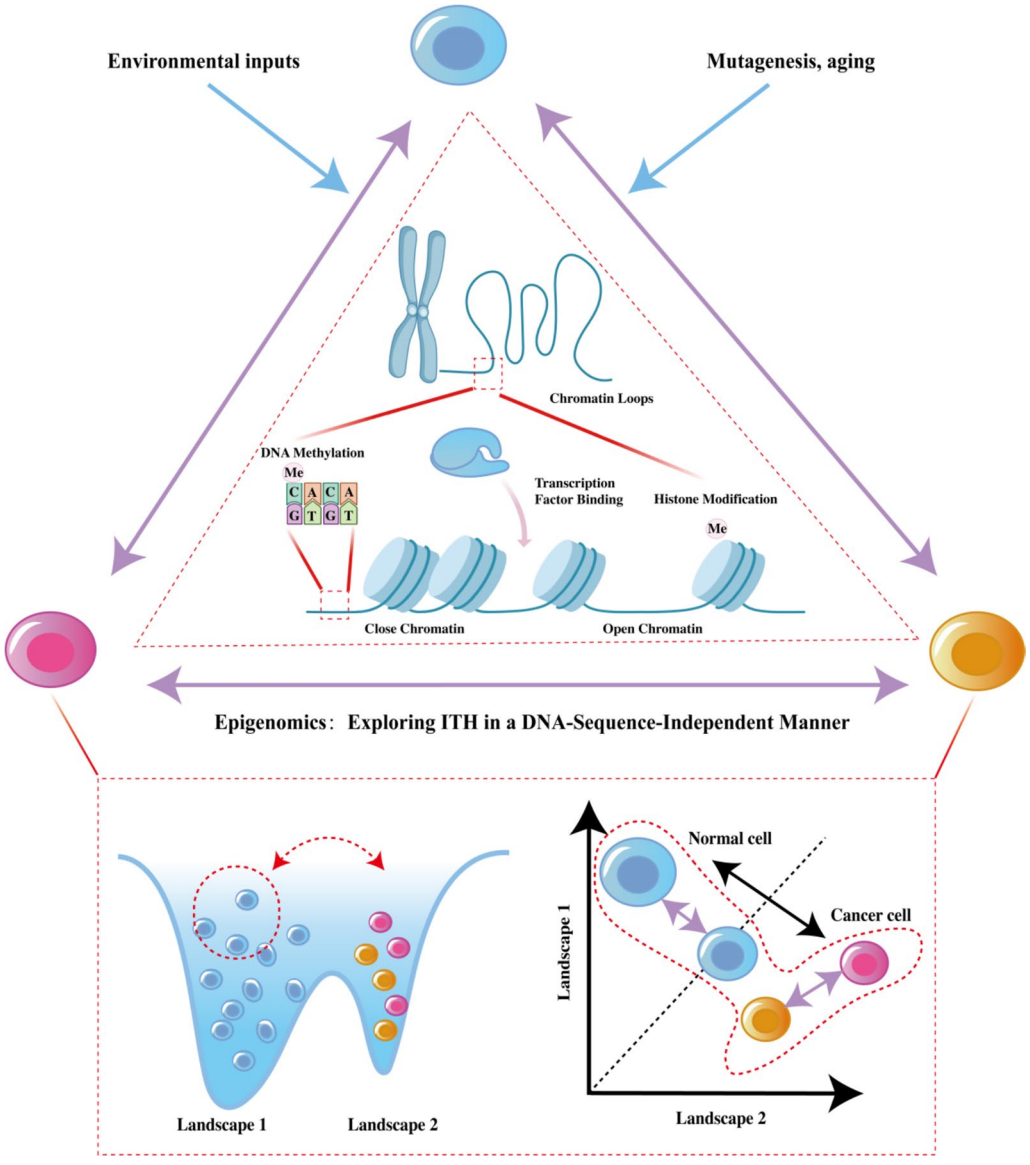

Fig. 5 Epigenomics: uncovering the regulatory landscape of tumor heterogeneity

relation between a transcription factor and peak-to-gene linkages (like linkage RUNX1 related elements regulates CD69) in mixed-phenotype acute leukemias (MPALs) [37]. Clinically, targeting chromatin regulators—such as DNA methylation enzymes, histone-modifying enzymes, and chromatin remodeling complexes (e.g., mammalian SWI/SNF)—holds therapeutic promise. Alterations in these complexes influence immune checkpoint therapy responses in clear cell renal cell carcinoma [15]. Additionally, glioblastoma stem cells (GSCs) rely on epigenetic regulation via EZH2 and KDM enzymes, which modulate drug resistance and recurrence. Targeting histone demethylases (e.g., KDM5A/B) significantly sensitizes resistant tumors to therapies [57]. These results suggest us intervene histone demethylase (KDM) and methyltransferase could mediate degree of drug resistance of glioblastoma for its therapy. Coincidently, KDM5 is proven correlating to therapeutic resistance especially endocrine resistance in breast cancer. Silencing or inhibition of KMD5 in breast tumors promotes sensitivity for anti-estrogens therapy via regulating estrogen receptor (ER) signaling and reducing its transcriptional heterogeneity [42]. To date, a higher level of KDM5B is undoubtedly associated with poor prognosis and more complex heterogeneity in clinical cancers. These publications together repetitively confirm the possible applications of epigenetics in cancer therapy and identify KDM5A/B as significant modulating factors during this process. Despite challenges such as low signal-to-noise ratios and sparse data matrices, recent advances in multi-omics

integration and computational deconvolution have enabled the mapping of epigenetic states to gene expression and phenotype. In summary, epigenomics uncovers a critical non-genetic layer of ITH, revealing how tumors exploit regulatory plasticity to sustain growth, evade treatment, and adapt under selective pressure. Epigenetic profiling not only enhances our mechanistic understanding of cancer but also provides actionable targets for epigenetic therapies and biomarker-driven interventions.

Proteomics: profiling functional diversity in cancer cells

Proteomics involves the large-scale study of proteins within biological systems, providing direct insights into cellular functions. Unlike genomics or transcriptomics, which indicate regulatory potentials, proteomics directly captures the functional outcomes of gene expression, such as protein abundance, post-translational modifications (PTMs), and protein–protein interactions, offering essential perspectives on ITH [65]. Proteomics techniques have significantly evolved, including two-dimensional gel electrophoresis (2DE), isoelectric focusing (IEF), liquid chromatography-tandem mass spectrometry (LC–MS/MS), and tandem time-of-flight mass spectrometry (TOF–MS) [1, 7, 11, 31, 94]. However, clinical translation of proteomics has lagged behind genomic approaches, partly due to technical complexity and cost. Recent studies have expanded the clinical relevance of proteomics. For instance, Nusinow et al. [73] performed mass spectrometry (MS)-based proteomic profiling of 375 cancer cell lines within the Cancer Cell Line Encyclopedia (CCLE) [73]. Approximately 50 proteins were found altered in microsatellite instability (MSI)-positive cells, partially aligning with RNA-seq data from corresponding MSI colorectal cancers in The Cancer Genome Atlas (TCGA) [55, 56, 90]. These MSI-associated proteomic changes included alterations in MutL and MutS complexes, reduced H3K4 methylation, and altered ribosomal protein profiles mediated by SKI complexes. Public resources for these datasets include the CCLE (https://gygi.med.harvard.edu/publications/ccle) and TCGA databases (https://tcgadata.nci.nih.gov/docs/publications/tcga/). Proteomics also supports the identification of b iomarkers and altered protein signatures associated with cancer progression, providing targets for addressing ITH. Given that protein function can be regulated through PTMs, alternative splicing, degradation, and activation, combining mass spectrometry results with computational analyses can reveal mechanisms underlying cancer development and progression [22, 76]. Several advanced MS-based techniques have emerged, including bottom-up proteomics for comprehensive biological profiling, selected reaction monitoring (SRM), multiple reaction monitoring (MRM), parallel reaction monitoring (PRM), data-independent acquisition (DIA) for quantitative analysis, data-dependent acquisition (DDA) for extensive quantification, and multi-dimensional chromatography for improved functional proteomics characterization [22, 26, 51, 68, 71, 78, 104]. In ovarian cancer, combined analyses using 2DE, MS, and immunohistochemistry identified significant changes in proteins such as galectin-3, retinol-binding protein-1, phosphatidylethanolamine-binding protein, annexin-5, glutathione *S*-transferase A-2, and calgranulin. These proteins correlated with cancer progression and were similarly altered in other solid tumors [92]. Additional proteomic investigations across different stages of ovarian cancer have identified protein signatures useful for evaluating aggressiveness and clinical outcomes [3, 24, 60]. Clinically, proteomics facilitates the identification of actionable biomarkers and therapeutic targets. For instance, reduced total and phosphorylated EGFR levels following gefitinib treatment indicate therapeutic responsiveness, whereas elevated levels suggest resistance mediated through pathways involving AKT. Similarly, declines in c-Kit and PDGFR during imatinib treatment in ovarian cancer correlate with adverse effects such as gastrointestinal toxicity and fatigue. Nonetheless, the clinical implementation of proteomic biomarkers requires further validation through rigorous trials [10]. In summary, proteomics complements nucleic acid-based profiling by offering functional insights into tumor biology and heterogeneity. Advances in analytical instrumentation, bioinformatics tools, and biomarker discovery significantly enhance the clinical utility of proteomics in precision oncology, guiding therapeutic strategies and improving cancer diagnosis and treatment outcomes.

Radiomics and radiogenomics: non-invasive assessment of tumor heterogeneity

Radiomics is an emerging research field employing computational algorithms to extract quantitative, high-dimensional features from medical imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). Radiomics-derived features, such as shape, intensity, texture, and wavelet transforms, serve as imaging phenotypes that reflect underlying ITH [44, 80]. The standard radiomics workflow consists of medical image acquisition, region-of-interest (ROI delineation (manual or automatic, feature extraction, data management, and personalized analytical modeling. Significantly, the dataset for imaging collections requires at least 10 examinations for one sample, as for ROI, it could be circled manually or automatically. Typically, datasets for radiomics analysis require multiple imaging examinations per patient sample to ensure accuracy and robustness. The core principle of radiomics is to translate complex tumor imaging data—including morphology, pixel/voxel

intensity, grayscale values, and gradient patterns—into quantitative digital biomarkers that capture tumor heterogeneity [58]. Radiogenomics, or imaging genomics, expands this concept by linking radiomic imaging phenotypes to genomic expression profiles. Once established, radiomics and radiogenomics datasets facilitate various clinical applications, including cancer detection, tumor classification, treatment stratification, prognosis prediction, and disease monitoring [63]. Advanced artificial intelligence (AI) models further enhance radiomics by correlating imaging features with genomic characteristics (gene expression, mutation status, heterogeneity), serum biomarkers, histological features, patient clinical history, and overall survival outcomes [5, 36, 44]. Public repositories such as The Cancer Imaging Archive (http://www.cancerimagingarchive.net) and initiatives from the Quantitative Imaging Network (QIN, http://imaging.cancer.gov/programsandresources/specializedinitiatives/qin) support standardized data sharing and promote collaborative analyses [45, 46]. A recent clinical study developed a radiomic model to assess $CD8^+$ immune cell infiltration, predicting responses to immunotherapy in patients with aggressive solid tumors [89]. Eight radiomic features—including first-order intensity measures, second-order grayscale characteristics, ROI location (adenopathy and head/neck region), and imaging acquisition parameters—were validated against CD8 gene expression data, successfully distinguishing immune-inflamed from immune-desert tumors ($p < 0.0001$). Among patients receiving immune checkpoint inhibitors, higher baseline radiomic scores correlated positively with objective treatment responses and stable disease status at follow-up. This $CD8^+$ radiomic model was further validated across independent cohorts, highlighting its potential for predicting tumor immune phenotypes and clinical prognosis following anti-PD-1/PD-L1 therapies [32]. Another example in non-small cell lung cancer (NSCLC) utilized radiomics integrated with pathological immune profiling, distinguishing two immune-related tumor subgroups [91]. Tumors characterized by higher immune activation (high CD3+ T lymphocyte infiltration, low PD-L1 expression) displayed lower imaging intensities and higher texture heterogeneity, correlating with improved clinical outcomes. Conversely, tumors with immune-inhibitory features (low CD3+, high PD-L1) had higher CT density and reduced heterogeneity, associated with poor prognosis [21]. Similarly, radiogenomic approaches combining imaging with transcriptomics (RNA-seq) have been applied to NSCLC, revealing distinct molecular imaging signatures [2]. Radiogenomics has also proven valuable in breast cancer studies comparing ultrasound imaging to RNA-seq-derived gene expression profiles [77]. Pathway and network analyses demonstrate significant correlations between imaging features and gene expression alterations, such as the association of specific ultrasound features with *TEF1*, *TEF3*, *AREG*, *ARG3*, *FZD8*, *IGF1R*, and *CRIPAK* gene expression levels [77]. Despite significant potential, radiomics still faces technical challenges, including variability in image acquisition, lack of standardized protocols, and difficulties in feature interpretability. Ongoing research efforts focus on multi-center harmonization and the development of robust AI-driven models to overcome these limitations. In summary, radiomics and radiogenomics provide powerful, non-invasive methods for real-time characterization of ITH. These techniques have broad potential in clinical oncology for enhancing diagnostic accuracy, therapeutic stratification, and monitoring disease progression. Integration with other omics approaches promises further advances toward personalized cancer care by linking imaging phenotypes to underlying molecular and genomic mechanisms.

Microbiome: exploring host–microbe interactions in tumor heterogeneity

While microbial cells in the human body are approximately equal in number to somatic and germ cells, the collective genome of these microorganisms, termed the microbiome, significantly exceeds the complexity of the human genome [35]. Clinical studies have demonstrated that dietary patterns, lifestyle changes, and emotional stress gradually affect the composition of the microbiota, significantly influencing disease progression [16, 108]. Due to the exposure of human gastrointestinal, oral, and vaginal tracts to external environments, isolating and culturing specific microorganisms from mixed microbiota remains challenging. Recent advancements in next-generation sequencing (NGS) and computational technologies enable the characterization of microbial populations in a culture-independent manner using metagenomics. These approaches provide critical insights into microbial involvement in cancer initiation and progression [6]. Accumulating evidence suggests that microbiota and their toxic metabolites can induce DNA damage, inflammation, and immune dysregulation, thereby increasing cancer susceptibility and impairing therapeutic responses [6, 41]. Notably, Helicobacter pylori infection induces chronic gastritis, gastric ulcers, and even gastric adenocarcinoma via persistent inflammatory responses [52]. Similarly, hepatitis B virus (HBV) and hepatitis C virus (HCV) contribute to liver cancer, human papillomavirus (HPV) causes cancers of the reproductive tract, anus, and oropharynx, Epstein-Barr virus (EBV) leads to Hodgkin's and non-Hodgkin's lymphoma, and human T-cell lymphotropic virus type 1 (HTLV-1) is responsible for adult T-cell lymphoma. All these microorganisms are classified as Class 1 carcinogens by the International Agency for Research on Cancer (IARC). Interestingly, some studies

suggest that *H. pylori* infection might suppress gastric acid reflux and stabilize stomach pH, potentially reducing the risk of Barrett's esophagus and esophageal adenocarcinoma [99]. These contrasting findings underscore the complex roles of microbiota in either promoting or suppressing tumorigenesis, emphasizing the necessity of comprehensive metagenomic analysis to elucidate these mechanisms. Multiple studies comparing intestinal microbiota in colorectal cancer patients to healthy individuals have revealed decreased microbial diversity and altered microbial ecosystems, correlating with increased cancer risk [54, 66]. Mechanistically, IL-10 knockout gnotobiotic mice colonized exclusively by Bacteroides vulgatus exhibit moderate colonic tumorigenesis following azoxymethane (AOM) treatment, while silencing of MyD88, a key inflammatory adaptor protein, prevents cancer progression. These results highlight how chronic inflammation mediated by the microbiome significantly promotes cancer initiation and progression. Microbiota-induced DNA damage, either through direct microbial toxins or indirect production of reactive oxygen species (ROS), represents a critical driver of tumorigenesis [105, 111]. Excess dietary protein is metabolized by bacteria such as Firmicutes and Bacteroides species into harmful nitroso compounds and electrophilic catabolites, resulting in genomic instability and DNA alkylation [13, 19]. Additionally, bacterial nitroreductases and nitrate reductases involved in these metabolic processes also intensify inflammatory responses. Furthermore, specific bacterial species and their secreted factors can directly influence tumor-related signaling pathways. For example, Fusobacterium nucleatum secretes the adhesin FadA, activating the WNT/β-catenin signaling pathway and promoting cancer via methylation-mediated silencing of the APC gene. Likewise, enterotoxigenic Bacteroides fragilis (ETBF), Salmonella typhi, and H. pylori secrete virulence factors activating β-catenin, c-MYC, and JAK-STAT3 pathways, thereby enhancing tumor proliferation and metastasis [62, 101]. These observations suggest significant roles for microbiota in modulating ITH. Several potential microbiome-targeted therapeutic strategies are currently under investigation, including: (1) fecal microbiota transplantation (FMT) to enhance the efficacy of immune checkpoint inhibitors (anti-PD-1 and anti-PD-L1), (2) selective antibiotic therapy to inhibit specific harmful bacterial populations and reshape microbiota compositions, thereby improving chemotherapy outcomes; and (3) targeted modification of microbial enzymes to reduce chemotherapy toxicity or enhance drug absorption [61, 84]. Together, these findings demonstrate that the tumor-associated microbiome contributes to intra-tumoral heterogeneity by modulating immune responses, inflammatory signaling, and genomic stability, and may serve as a promising target for biomarker discovery and personalized therapeutic strategies within multi-omics frameworks.

Metabolomics: capturing metabolic signatures of tumor diversity

Tumor cells undergo significant metabolic reprogramming to sustain rapid growth, generate sufficient energy, produce abundant metabolic intermediates, and adapt effectively to a fluctuating microenvironment [12, 86]. Metabolomics, also termed metabolic profiling, characterizes metabolic alterations associated with cancer physiology and tumor progression [103]. Specifically, metabolomics involves real-time, quantitative analysis of metabolic responses in living systems arising from genetic or environmental modifications [102]. Metabolomic approaches encompass multiple analytical techniques, including mass spectrometry (MS), nuclear magnetic resonance (NMR), stable isotope-labeled dynamic metabolic profiling (SIDMAP), mass isotopomer distribution analysis (MIDA), electrochemical arrays (EC-array), hydrophobic interaction chromatography (HIC), Fourier transform infrared (FT-IR) microscopy, and capillary electrophoresis (CE) [25, 29, 43, 69, 75, 81]. Metabolomic analyses can be broadly categorized into untargeted (metabolic fingerprinting) methods, which compare experimental and control metabolite profiles, and targeted (metabolic profiling) methods, which employ isotope-labeled metabolites (e.g., 2H or 13C) to quantify specific analytes precisely [112]. Metabolomic analyses utilize diverse biological samples, including tissue biopsies, urine, sputum, serum, and fecal extracts, each reflecting distinct metabolic alterations. For instance, urine primarily reflects amino acid and nicotinamide pathways, fecal extracts indicate alterations in glucose, amino acids, lipids, and microbiota metabolism, while sputum predominantly reveals amino acid and energy metabolism pathways [81]. In one study employing LC–MS analysis of paired human prostate cancer samples, researchers reported increased NAD metabolites (NMN, NAD, NADP), elevated expression of genes involved in hexosamine biosynthesis (HK2, GFPT1, GNPNAT1, UAP1, OGT), enhanced fatty acid β-oxidation, and reduced expression of tumor suppressors (SIRP2, RND2, RND3). NAD metabolism enhances reactive oxygen species (ROS) production, hexosamine biosynthesis promotes glutamine uptake, and β-oxidation supplies energy, collectively accelerating prostate cancer proliferation [14]. Additionally, an accumulation of *S*-adenosylhomocysteine (SAH), *S*-adenosylmethionine (SAM), and glycine *N*-methyltransferase (GNMT)—an enzyme inhibited by miR-100-5p—was observed. GNMT mediates SAM-to-SAH conversion and is implicated as a susceptibility gene due to its role in genome instability through regulation of the SAM/SAH ratio and interactions with folate metabolism [82]. Another

metabolomics-based study involving 28 clinical patient-derived cancer cell lines (blood, breast, colon, lung, and stomach tumors) examined sensitivity to electron transport chain (ETC) inhibitors (piericidin, antimycin A, oligomycin, phenformin). Metabolomic analysis identified 19 key metabolites, including malate, citrate, fumarate, aspartate, and argininosuccinate, which share aspartate as a common precursor. Importantly, elevated intracellular aspartate counteracted ETC inhibition by promoting nucleotide biosynthesis through SLC1A3-mediated import (a glutamate-aspartate transporter). Compared to lactate or acylcarnitines, aspartate was significantly correlated with tumor hypoxia, indicating its potential utility as a metabolic marker for hypoxic conditions in glioblastoma. These findings suggest that hypoxia-induced growth suppression in tumors can be partially reversed by exogenous aspartate, presenting a potential therapeutic target for addressing tumor hypoxic heterogeneity. In conclusion, integrating metabolomics with other omics modalities in clinical oncology provides comprehensive insights into tumor biology, facilitating the design of personalized and multi-dimensional therapeutic strategies.

Cross-modal integration and convergent pathways in patient stratification

Each omics layer provides a distinct perspective on intratumoral heterogeneity, but recent studies highlight the importance of cross-modal integration in uncovering convergent pathways that guide functional tumor classification. Rather than being redundant, modalities like genomics, metabolomics, and radiomics often reveal orthogonal yet biologically connected insights, offering a multidimensional understanding of tumor behavior. For instance, the TRACERx renal study revealed chromosomal instability and driver mutations associated with clonal evolution trajectories [34]. When integrated with metabolomic profiling, these genomic subtypes exhibit distinct metabolic signatures, including enhanced fatty acid oxidation or glutamine dependence—underscoring metabolic reprogramming as a functional consequence of genomic instability. Likewise, IDH1/2 mutations, although identifiable through genomic analysis, correlate with the accumulation of the oncometabolite 2-hydroxyglutarate, supporting stratification by both mutation status and metabolic phenotype [100]. In radiogenomics, imaging features like heterogeneous texture or irregular boundaries have been linked to molecular alterations such as TP53 mutations and VEGF pathway activation [64]. These imaging-derived biomarkers allow for non-invasive prediction of genomic states and serve as surrogates when biopsy is impractical or longitudinal monitoring is required. Furthermore, integrating epigenomic and transcriptomic data with spatial proteomics has revealed shared immune evasion pathways—such as Wnt/β-catenin activation, consistently observed at chromatin, transcript, and protein levels across various cancers [49]. This convergence supports pathway-based rather than single-variant-based stratification. Collectively, these integrative approaches improve patient stratification by defining functional phenotypes that reflect both genetic alterations and dynamic expression or metabolic activity. Future models integrating multi-omics data should prioritize shared pathway signatures over isolated molecular events to enable more robust and clinically relevant classifications.

Emerging technologies in multi-omics profiling

In recent years, advanced technologies such as spatial transcriptomics, single-cell multi-omics, and CRISPR-based lineage tracing have substantially deepened our understanding of ITH. These platforms surpass traditional bulk multi-omics approaches by integrating spatial, temporal, and functional information to enable high-resolution molecular phenotyping. For example, spatial transcriptomics now permits the in situ mapping of gene expression while maintaining the native tissue architecture. Gulati et al. developed a multiscale cognitive framework that bridges the single-cell level and spatial tissue organization, highlighting the importance of cross-scale integration. They proposed that multi-scale omics integration represents a transformative paradigm for elucidating tissue homeostasis and disease mechanisms [38]. Similarly, Mara et al. employed spatial transcriptomics and single-cell sequencing to reveal pronounced subclonal heterogeneity and spatially distinct immune dysfunction in extramedullary lesions (EMDs) of multiple myeloma [47]. Their findings suggest that the spatial segregation of T-cell exhaustion from activation states may influence therapeutic efficacy, though the underlying mechanisms remain unclear. Together, these studies illustrate the potential of spatially resolved omics technologies to provide a multiscale systems biology perspective on tumor heterogeneity, offering new insights into tumor biology and therapeutic response.

The advent of single-cell multi-omics, including integrated transcriptome and chromatin accessibility profiling (e.g., TEA-seq, Paired-seq), has enabled high-resolution dissection of tumor ecosystems. For example, Zheng et al. identified the molecular signatures and spatial organization of functionally heterogeneous cancer cells in clear cell renal cell carcinoma (ccRCC) by combining single-cell multi-omics with spatial transcriptomics, offering new insights into intra-tumoral heterogeneity and informing precision treatment strategies. Concurrently, CRISPR-based lineage tracing—particularly CRISPR barcoding integrated with single-cell omics—has advanced significantly. These technologies are redefining tumor profiling by linking spatial origin,

clonal evolution, and molecular phenotype. Their incorporation into multi-omics workflows is critical for enhancing spatially resolved tumor classification, capturing therapy-induced clonal dynamics, and informing adaptive therapeutic interventions.

Conclusion and perspectives

ITH remains a major challenge in oncology, driving tumor evolution, therapeutic resistance, immune evasion, and disease recurrence. This review has summarized how multi-omics technologies—including genomics, transcriptomics, epigenomics, proteomics, metabolomics, radiomics, and microbiomics—provide complementary insights into the genetic, epigenetic, functional, and spatial complexity of tumors. Integrated multi-omics approaches facilitate a comprehensive systems-level analysis of ITH, significantly advancing both biological understanding and clinical management. A critical advantage of multi-omics methods is their ability to transcend single-dimensional perspectives, offering dynamic and high-resolution mapping of tumor ecosystems. Genomics identifies clonal drivers and mutational signatures; single-cell transcriptomics reveals lineage hierarchies and cellular plasticity; epigenomics elucidates regulatory mechanisms; proteomics captures functional diversity; metabolomics characterizes biochemical states in real-time; radiomics provides non-invasive spatial assessments; and microbiomics contextualizes host-environment interactions. Together, these techniques represent a paradigm shift towards integrative oncology.

Despite significant progress in multi-omics strategies for characterizing intra-tumoral heterogeneity, several challenges continue to hinder their translational potential. A primary obstacle is data harmonization, as omics datasets are often generated using diverse protocols, instrumentation, and preprocessing pipelines. This heterogeneity undermines integrative analyses and limits reproducibility across studies. Additionally, imputing missing data in high-dimensional contexts remains technically challenging, with many current statistical methods failing to preserve underlying biological signals. From an implementation perspective, economic barriers also constrain broader adoption. Comprehensive multi-omics profiling requires substantial investment in sequencing, instrumentation, computational resources, and skilled personnel—posing difficulties for resource-limited settings. Regulatory uncertainty further impedes clinical translation, as few clear guidelines exist for the approval of multi-omics-based diagnostics or stratification tools. Concerns about data privacy, algorithm interpretability, and generalizability across diverse patient populations remain unresolved.

To advance clinical translation, it will be essential to develop standardized data formats, interoperable analytic

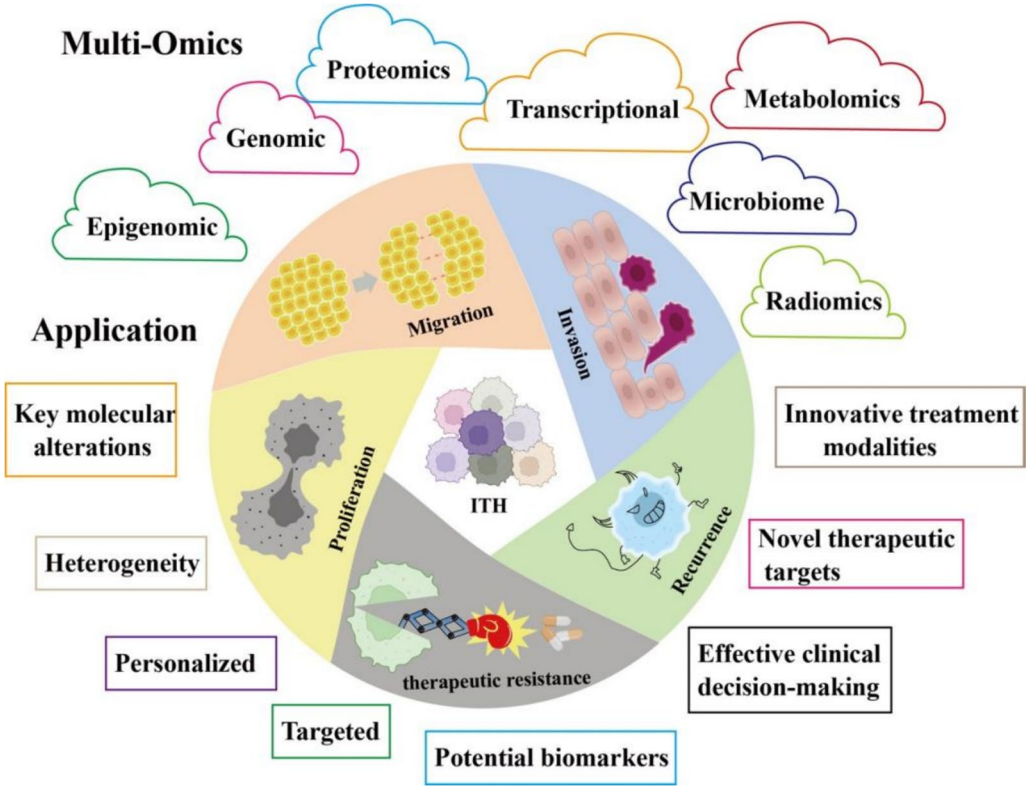

Fig. 6 ITH and application of multi-OMICS approaches in cancer biology

platforms, and robust cross-modal imputation algorithms. International consortia should prioritize harmonization initiatives and the creation of benchmark datasets. Concurrently, advances in federated learning and privacy-preserving computation may help address ethical and regulatory challenges. Finally, future studies should incorporate cost-effectiveness analyses and focus on developing scalable, real-world models to enable broader clinical integration.

Despite these limitations, recent advances in machine learning, spatial single-cell technologies, and biobank-integrated clinical trials have accelerated the translation of multi-omics into clinical practice. Emerging methodologies—such as multimodal deep learning, dynamic modeling of ITH, and longitudinal sample collection—promise further insights into tumor evolution over space and time. Additionally, the increasing availability of large-scale datasets from initiatives such as TCGA, CPTAC, and ICGC-ARGO provides extensive resources for validation studies and biomarker identification.

In summary, recognizing ITH as a multi-layered, adaptive phenomenon and decoding it through integrated multi-omics analyses represent a transformative approach in precision oncology. As analytical methods continue to mature and costs decrease, multi-omics-guided profiling of ITH is expected to become standard clinical practice, enhancing early diagnosis, dynamic risk stratification, treatment selection, and monitoring of therapeutic resistance. Achieving this vision requires sustained interdisciplinary collaboration to fully exploit the potential of integrated multi-omics for improved cancer patient care (Fig. 6).

Abbreviations

2DE	Two-dimensional gel electrophoresis
AML	Acute myeloid leukemia
AOM	Azoxymethane
ATAC-seq	Assay for transposase-accessible chromatin with high-throughput sequencing
BCR	B-cell receptor
BKT	Bruton's tyrosine kinase
CCFs	Cancer cell fractions
CCLE	Cancer Cell Line Encyclopedia
ccRCC	Clear-cell renal cell carcinoma
CE	Capillary electrophoresis
CITE-seq	Cellular indexing of transcriptomic and epitopes by sequencing
CLL	Chronic lymphocytic leukemia
CNAs	Copy number alterations
CRA	Colorectal adenoma
CRCs	Colorectal cancers
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CT	Computed tomography
ctDNA	Circulating tumor DNA
DCs	Dendritic cells
DDA	Data dependent acquisition
DIA	Data independent acquisition
DLP	Direct library preparation
DNMT	DNA methyltransferase
EBV	Epstein-Barr virus
EC-array	Electrochemistry array
EOC	Epithelial ovarian cancers
ER	Estrogen receptor
E-scape	Evolutionary landscape
ETC	Electron transport chain
EWAS	Epigenome-wide association studies
FNA	Fine needle aspirate
FT-IR	Fourier transform infrared microscopy
GI	Gastrointestinal
GSC	Glioblastoma stem cell
GWAS	Genome-wide association study
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIC	Hydrophobic interaction chromatography
HPV	Human papillomavirus
HTLV1	Human T-cell lymphotropic virus type 1
IARC	International Agency for Research on Cancer
ICR	Imprinting control region
IEF	Isoelectric focusing
ITH	Intra-tumoral heterogeneity
KDM	Histone demethylase
LC–MS/MS	Liquid chromatograph-tandem mass spectrometer
LOH	Loss of heterozygosity
M-DLP	Microfluidic-based DLP
MIDA	Mass isotopomer distribution analysis
MPALs	Mixed-phenotype acute leukemias
MRI	Magnetic resonance imaging
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MSI	Microsatellite instable
mSWI/SNF	Mammalian Switch/Sucrose-Nonfermentable
NAF	Nipple aspirate fluid
NGS	Next generation sequencing
NMR	Nuclear magnetic resonance
NSCLC	Non-small cell lung cancer
OESC	Ovarian epithelial serous cystadenocarcinoma
PET-CT	Positron computed tomography with computed tomography
PET-MR	Positron computed tomography with magnetic resonance
PRM	Parallel reaction monitoring
PTMs	Post-translational modifications
QIN	Quantitative Imaging Network
ROI	Region of interest
ROS	Reactive oxygen species
SAH	*S*-Adenosylhomoserine
SAM	*S*-Adenosylmethionine
scWGS	Single-cell WGS
seqFISH	Sequential fluorescence in situ hybridization
SIDMAP	Sable isotope-labeled dynamic metabolic profiling
SNS	Single nucleus sequencing
SRM	Selected reaction monitoring
TAMs	Tumor-associated macrophages
TCGA	The Cancer Genome Atlas
TF	Transcriptional factor
TME	Tumor microenvironment
TOF–MS	Tandem time-of-flight mass spectrometer
US	Ultrasound
VAF	Variant allele frequency
WES	Whole-exome sequencing
WGA	Whole genome amplification
wGII	Weighted genome instability index
WGS	Whole-genome sequencing

Acknowledgements
Not applicable.

Author contributions
Liping Wang contributed conception and design of the study; Mengmeng Dong wrote the first draft of the manuscript; Yu Zhang, Yueli Rao and Zhen Wang wrote sections of the manuscript and provided the critical revisions. All authors revised the manuscript and approved the submitted version.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 7 May 2025 / Accepted: 6 August 2025
Published online: 29 August 2025

References

1. Arslan T, Pan Y, Mermelekas G, et al. SubCellBarCode: integrated workflow for robust spatial proteomics by mass spectrometry. Nat Protoc. 2022;17(8):1832–67. https://doi.org/10.1038/s41596-022-00699-2.
2. Bakr S, Gevaert O, Echegaray S, et al. A radiogenomic dataset of non-small cell lung cancer. Sci Data. 2018;5: 180202. https://doi.org/10.1038/sdata.2018.202.
3. Bear AS, Nadler RB, O'Hara MH, et al. Natural TCRs targeting KRASG12V display fine specificity and sensitivity to human solid tumors. J Clin Invest. 2024. https://doi.org/10.1172/JCI175790.
4. Bell CC, Fennell KA, Chan YC, et al. Targeting enhancer switching overcomes non-genetic drug resistance in acute myeloid leukaemia. Nat Commun. 2019;10(1):2723. https://doi.org/10.1038/s41467-019-10652-9.
5. Bera K, Braman N, Gupta A, et al. Predicting cancer outcomes with radiomics and artificial intelligence in radiology. Nat Rev Clin Oncol. 2022;19(2):132–46. https://doi.org/10.1038/s41571-021-00560-7.
6. Bhatt AP, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. CA Cancer J Clin. 2017;67(4):326–44. https://doi.org/10.3322/caac.21398.
7. Bian Y, Zheng R, Bayer FP, et al. Robust, reproducible and quantitative analysis of thousands of proteomes by micro-flow LC-MS/MS. Nat Commun. 2020;11(1):157. https://doi.org/10.1038/s41467-019-13973-x.
8. Biswas A, Sahoo S, Riedlinger GM, et al. Transcriptional state dynamics lead to heterogeneity and adaptive tumor evolution in urothelial bladder carcinoma. Commun Biol. 2023;6(1):1292. https://doi.org/10.1038/s42003-023-05668-3.
9. Black JRM, McGranahan N. Genetic and non-genetic clonal diversity in cancer evolution. Nat Rev Cancer. 2021;21(6):379–92. https://doi.org/10.1038/s41568-021-00336-2.
10. Bonsack F, Sukumari-Ramesh S. Differential cellular expression of galectin-1 and galectin-3 after intracerebral hemorrhage. Front Cell Neurosci. 2019;13:157. https://doi.org/10.3389/fncel.2019.00157.
11. Cakir B, Gulseren I. Identification of novel proteins from black cumin seed meals based on 2D gel electrophoresis and MALDI-TOF/TOF-MS analysis. Plant Foods Hum Nutr. 2019;74(3):414–20. https://doi.org/10.1007/s11130-019-00751-9.
12. Cao L, Wu J, Qu X, et al. Glycometabolic rearrangements–aerobic glycolysis in pancreatic cancer: causes, characteristics and clinical applications. J Exp Clin Cancer Res. 2020;39(1):267. https://doi.org/10.1186/s13046-020-01765-x.
13. Cao Y, Oh J, Xue M, et al. Commensal microbiota from patients with inflammatory bowel disease produce genotoxic metabolites. Science. 2022;378(6618):eabm3233. https://doi.org/10.1126/science.abm3233.
14. Castelli S, Ciccarone F, Tavian D, et al. ROS-dependent HIF1alpha activation under forced lipid catabolism entails glycolysis and mitophagy as mediators of higher proliferation rate in cervical cancer cells. J Exp Clin Cancer Res. 2021;40(1):94. https://doi.org/10.1186/s13046-021-01887-w.
15. Centore RC, Sandoval GJ, Soares LMM, et al. Mammalian SWI/SNF chromatin remodeling complexes: emerging mechanisms and therapeutic strategies. Trends Genet. 2020;36(12):936–50. https://doi.org/10.1016/j.tig.2020.07.011.
16. Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol. 2019;30(12):2012. https://doi.org/10.1093/annonc/mdz224.
17. Chen D, Zhang R, Huang X, et al. Mri-derived radiomics assessing tumor-infiltrating macrophages enable prediction of immune-phenotype, immunotherapy response and survival in glioma. Biomark Res. 2024;12(1):14. https://doi.org/10.1186/s40364-024-00560-6.
18. Chen G, Zhu W, Liu Y, et al. The clonal heterogeneity of colon cancer with liver metastases. J Gastroenterol. 2023;58(7):642–55. https://doi.org/10.1007/s00535-023-01989-6.
19. Chen J, Li T, Liang J, et al. Current status of intratumour microbiome in cancer and engineered exogenous microbiota as a promising therapeutic strategy. Biomed Pharmacother. 2022;145: 112443. https://doi.org/10.1016/j.biopha.2021.112443.
20. Chihara D, Balakrishnan K, Masand G, et al. Test-the-test: clinical utility of comprehensive whole exome sequencing and RNA-seq for patients with lymphoma. Blood. 2023;142:7155.
21. Choy G, Khalilzadeh O, Michalski M, et al. Current applications and future impact of machine learning in radiology. Radiology. 2018;288(2):318–28. https://doi.org/10.1148/radiol.2018171820.
22. Cifani P, Kentsis A. Towards comprehensive and quantitative proteomics for diagnosis and therapy of human disease. Proteomics. 2017. https://doi.org/10.1002/pmic.201600079.
23. Cirkovic A, Garovic V, Milin Lazovic J, et al. Systematic review supports the role of DNA methylation in the pathophysiology of preeclampsia: a call for analytical and methodological standardization. Biol Sex Differ. 2020;11(1):36. https://doi.org/10.1186/s13293-020-00313-8.
24. Cousin S, Guegan JP, Shitara K, et al. Identification of microenvironment features associated with primary resistance to anti-PD-1/PD-L1 + antiangiogenesis in gastric cancer through spatial transcriptomics and plasma proteomics. Mol Cancer. 2024;23(1):197. https://doi.org/10.1186/s12943-024-02092-x.
25. Cui P, Li X, Huang C, et al. Metabolomics-driven discovery of therapeutic targets for cancer cachexia. J Cachexia Sarcopenia Muscle. 2024;15(3):781–93. https://doi.org/10.1002/jcsm.13465.
26. Dai C, Pfeuffer J, Wang H, et al. Quantms: a cloud-based pipeline for quantitative proteomics enables the reanalysis of public proteomics data. Nat Methods. 2024;21(9):1603–7. https://doi.org/10.1038/s41592-024-02343-1.
27. Davalos V, Esteller M. Cancer epigenetics in clinical practice. CA Cancer J Clin. 2023;73(4):376–424. https://doi.org/10.3322/caac.21765.
28. De Sarkar N, Patton RD, Doebley AL, et al. Nucleosome patterns in circulating tumor DNA reveal transcriptional regulation of advanced prostate cancer phenotypes. Cancer Discov. 2023;13(3):632–53. https://doi.org/10.1158/2159-8290.CD-22-0692.
29. DeBerardinis RJ, Keshari KR. Metabolic analysis as a driver for discovery, diagnosis, and therapy. Cell. 2022;185(15):2678–89. https://doi.org/10.1016/j.cell.2022.06.029.
30. Dietzen M, Zhai H, Lucas O, et al. Replication timing alterations are associated with mutation acquisition during breast and lung cancer evolution. Nat Commun. 2024;15(1): 6039. https://doi.org/10.1038/s41467-024-50107-4.
31. Ding Z, Wang N, Ji N, et al. Proteomics technologies for cancer liquid biopsies. Mol Cancer. 2022;21(1):53. https://doi.org/10.1186/s12943-022-01526-8.
32. El Naqa I, Ten Haken RK. Can radiomics personalise immunotherapy? Lancet Oncol. 2018;19(9):1138–9. https://doi.org/10.1016/S1470-2045(18)30429-7.
33. Flavahan WA, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. Science. 2017. https://doi.org/10.1126/science.aal2380.
34. Fu X, Zhao Y, Lopez JI, et al. Spatial patterns of tumour growth impact clonal diversification in a computational model and the TRACERx Renal study. Nat Ecol Evol. 2022;6(1):88–102. https://doi.org/10.1038/s41559-021-01586-x.
35. Ghaddar B, Biswas A, Harris C, et al. Tumor microbiome links cellular programs and immunity in pancreatic cancer. Cancer Cell. 2022;40(10):1240-1253 e1245. https://doi.org/10.1016/j.ccell.2022.09.009.
36. Gillies RJ, Beyer T. PET and MRI: is the whole greater than the sum of its parts? Cancer Res. 2016;76(21):6163–6. https://doi.org/10.1158/0008-5472.CAN-16-2121.
37. Granja JM, Klemm S, McGinnis LM, et al. Single-cell multiomic analysis identifies regulatory programs in mixed-phenotype acute leukemia. Nat Biotechnol. 2019;37(12):1458–65. https://doi.org/10.1038/s41587-019-0332-7.
38. Gulati GS, D'Silva JP, Liu Y, et al. Profiling cell identity and tissue architecture with single-cell and spatial transcriptomics. Nat Rev Mol Cell Biol. 2025;26(1):11–31. https://doi.org/10.1038/s41580-024-00768-2.
39. Haupt S, Caramia F, Klein SL, et al. Sex disparities matter in cancer development and therapy. Nat Rev Cancer. 2021;21(6):393–407. https://doi.org/10.1038/s41568-021-00348-y.

40. Hay AD, Kessler NJ, Gebert D, et al. Epigenetic inheritance is unfaithful at intermediately methylated CpG sites. Nat Commun. 2023;14(1):5336. https://doi.org/10.1038/s41467-023-40845-2.
41. Helmink BA, Khan MAW, Hermann A, et al. The microbiome, cancer, and cancer therapy. Nat Med. 2019;25(3):377–88. https://doi.org/10.1038/s41591-019-0377-7.
42. Hinohara K, Wu HJ, Vigneau S, et al. KDM5 histone demethylase activity links cellular transcriptomic heterogeneity to therapeutic resistance. Cancer Cell. 2018;34(6):939-953 e939. https://doi.org/10.1016/j.ccell.2018.10.014.
43. His M, Gunter MJ, Keski-Rahkonen P, et al. Application of metabolomics to epidemiologic studies of breast cancer: new perspectives for etiology and prevention. J Clin Oncol. 2024;42(1):103–15. https://doi.org/10.1200/JCO.22.02754.
44. Incoronato M, Aiello M, Infante T, et al. Radiogenomic analysis of oncological data: a technical survey. Int J Mol Sci. 2017. https://doi.org/10.3390/ijms18040805.
45. Jha AK, Mithun S, Purandare NC, et al. Radiomics: a quantitative imaging biomarker in precision oncology. Nucl Med Commun. 2022;43(5):483–93. https://doi.org/10.1097/MNM.0000000000001543.
46. Jha AK, Mithun S, Sherkhane UB, et al. Emerging role of quantitative imaging (radiomics) and artificial intelligence in precision oncology. Explor Target Antitumor Ther. 2023;4(4):569–82. https://doi.org/10.37349/etat.2023.00153.
47. John M, Helal M, Duell J, et al. Spatial transcriptomics reveals profound subclonal heterogeneity and T-cell dysfunction in extramedullary myeloma. Blood. 2024;144(20):2121–35. https://doi.org/10.1182/blood.2024024590.
48. Jun SH, Toosi H, Mold J, et al. Reconstructing clonal tree for phylo-phenotypic characterization of cancer using single-cell transcriptomics. Nat Commun. 2023;14(1):982. https://doi.org/10.1038/s41467-023-36202-y.
49. Laisne M, Lupien M, Vallot C. Epigenomic heterogeneity as a source of tumour evolution. Nat Rev Cancer. 2025;25(1):7–26. https://doi.org/10.1038/s41568-024-00757-9.
50. Laks E, McPherson A, Zahn H, et al. Clonal decomposition and DNA replication states defined by scaled single-cell genome sequencing. Cell. 2019;179(5):1207-1221 e1222. https://doi.org/10.1016/j.cell.2019.10.026.
51. Leduc A, Khoury L, Cantlon J, et al. Massively parallel sample preparation for multiplexed single-cell proteomics using nPOP. Nat Protoc. 2024. https://doi.org/10.1038/s41596-024-01033-8.
52. Lee YC, Chiang TH, Chiu HM, et al. Screening for *Helicobacter pylori* to prevent gastric cancer: a pragmatic randomized clinical trial. JAMA. 2024. https://doi.org/10.1001/jama.2024.14887.
53. Li L, Bowling S, McGeary SE, et al. A mouse model with high clonal barcode diversity for joint lineage, transcriptomic, and epigenomic profiling in single cells. Cell. 2023;186(23):5183-5199 e5122. https://doi.org/10.1016/j.cell.2023.09.019.
54. Li S, Xia H, Wang Z, et al. Intratumoral microbial heterogeneity affected tumor immune microenvironment and determined clinical outcome of HBV-related HCC. Hepatology. 2023;78(4):1079–91. https://doi.org/10.1097/HEP.0000000000000427.
55. Li Y, Wang B, Ma F, et al. Proteomic characterization of the colorectal cancer response to chemoradiation and targeted therapies reveals potential therapeutic strategies. Cell Rep Med. 2023;4(12): 101311. https://doi.org/10.1016/j.xcrm.2023.101311.
56. Li Y, Wang B, Yang W, et al. Longitudinal plasma proteome profiling reveals the diversity of biomarkers for diagnosis and cetuximab therapy response of colorectal cancer. Nat Commun. 2024;15(1):980. https://doi.org/10.1038/s41467-024-44911-1.
57. Liau BB, Sievers C, Donohue LK, et al. Adaptive chromatin remodeling drives glioblastoma stem cell plasticity and drug tolerance. Cell Stem Cell. 2017;20(2):233-246.e237. https://doi.org/10.1016/j.stem.2016.11.003.
58. Lin DF, Li HL, Liu T, et al. Radiomic signatures associated with tumor immune heterogeneity predict survival in locally recurrent nasopharyngeal carcinoma. J Natl Cancer Inst. 2024;116(8):1294–302. https://doi.org/10.1093/jnci/djae081.
59. Lin J, Shen M, Xiao W, et al. Common and rare variants in genetic susceptibility analysis of mature B-cell neoplasm subtypes by whole exome sequencing. Leukemia. 2024;38(9):2059–63. https://doi.org/10.1038/s41375-024-02332-5.
60. Lin XT, Luo YD, Mao C, et al. Integrated ubiquitomics characterization of hepatocellular carcinomas. Hepatology. 2024. https://doi.org/10.1097/HEP.0000000000001096.
61. Liu L, Shah K. The potential of the gut microbiome to reshape the cancer therapy paradigm: a review. JAMA Oncol. 2022;8(7):1059–67. https://doi.org/10.1001/jamaoncol.2022.0494.
62. Lu R, Wu S, Zhang YG, et al. Enteric bacterial protein AvrA promotes colonic tumorigenesis and activates colonic beta-catenin signaling pathway. Oncogenesis. 2014;3(6): e105. https://doi.org/10.1038/oncsis.2014.20.
63. Mayerhoefer ME, Materka A, Langs G, et al. Introduction to radiomics. J Nucl Med. 2020;61(4):488–95. https://doi.org/10.2967/jnumed.118.222893.
64. Mendes Serrao E, Klug M, Moloney BM, et al. Current status of cancer genomics and imaging phenotypes: what radiologists need to know. Radiol Imaging Cancer. 2023;5(6): e220153. https://doi.org/10.1148/rycan.220153.
65. Messner CB, Demichev V, Muenzner J, et al. The proteomic landscape of genome-wide genetic perturbations. Cell. 2023;186(9):2018–34. https://doi.org/10.1016/j.cell.2023.03.026.
66. Mira-Pascual L, Cabrera-Rubio R, Ocon S, et al. Microbial mucosal colonic shifts associated with the development of colorectal cancer reveal the presence of different bacterial and archaeal biomarkers. J Gastroenterol. 2015;50(2):167–79. https://doi.org/10.1007/s00535-014-0963-x.
67. Moujaess E, Kourie HR, Ghosn M. Cancer patients and research during COVID-19 pandemic: a systematic review of current evidence. Crit Rev Oncol Hematol. 2020;150: 102972. https://doi.org/10.1016/j.critrevonc.2020.102972.
68. Mund A, Brunner AD, Mann M. Unbiased spatial proteomics with single-cell resolution in tissues. Mol Cell. 2022;82(12):2335–49. https://doi.org/10.1016/j.molcel.2022.05.022.
69. Nagana Gowda GA, Raftery D. NMR metabolomics methods for investigating disease. Anal Chem. 2023;95(1):83–99. https://doi.org/10.1021/acs.analchem.2c04606.
70. Nam AS, Chaligne R, Landau DA. Integrating genetic and non-genetic determinants of cancer evolution by single-cell multi-omics. Nat Rev Genet. 2021;22(1):3–18. https://doi.org/10.1038/s41576-020-0265-5.
71. Navin N, Kendall J, Troge J, et al. Tumourevolution inferred by single-cell sequencing. Nature 2011;472(7341):90–94.https://doi.org/10.1038/nature09807.
72. Norton ES, Whaley LA, Jones VK, et al. Cell-specific cross-talk proteomics reveals cathepsin B signaling as a driver of glioblastoma malignancy near the subventricular zone. Sci Adv. 2024;10(32): eadn1607. https://doi.org/10.1126/sciadv.adn1607.
73. Nusinow DP, Szpyt J, Ghandi M, et al. Quantitative proteomics of the cancer cell line encyclopedia. Cell. 2020;180(2):387-402 e316. https://doi.org/10.1016/j.cell.2019.12.023.
74. Oliva M, Demanelis K, Lu Y, et al. DNA methylation QTL mapping across diverse human tissues provides molecular links between genetic variation and complex traits. Nat Genet. 2023;55(1):112–22. https://doi.org/10.1038/s41588-022-01248-z.
75. Pakkir Shah AK, Walter A, Ottosson F, et al. Statistical analysis of feature-based molecular networking results from non-targeted metabolomics data. Nat Protoc. 2024. https://doi.org/10.1038/s41596-024-01046-3.
76. Pan S, Chen R. Pathological implication of protein post-translational modifications in cancer. Mol Aspects Med. 2022;86: 101097. https://doi.org/10.1016/j.mam.2022.101097.
77. Park AY, Han MR, Park KH, et al. Radiogenomic analysis of breast cancer by using B-mode and vascular US and RNA sequencing. Radiology. 2020;295(1):24–34. https://doi.org/10.1148/radiol.2020191368.
78. Petrosius V, Aragon-Fernandez P, Uresin N, et al. Exploration of cell state heterogeneity using single-cell proteomics through sensitivity-tailored data-independent acquisition. Nat Commun. 2023;14(1):5910. https://doi.org/10.1038/s41467-023-41602-1.
79. Plusquin M, Guida F, Polidoro S, et al. DNA methylation and exposure to ambient air pollution in two prospective cohorts. Environ Int. 2017;108:127–36. https://doi.org/10.1016/j.envint.2017.08.006.
80. Porcu M, Solinas C, Mannelli L, et al. Radiomics and "radi-...omics" in cancer immunotherapy: a guide for clinicians. Crit Rev Oncol Hematol. 2020;154:103068. https://doi.org/10.1016/j.critrevonc.2020.103068.
81. Ranjan R, Sinha N. Nuclear magnetic resonance (NMR)-based metabolomics for cancer research. NMR Biomed. 2019;32(10): e3916. https://doi.org/10.1002/nbm.3916.
82. Ren S, Shao Y, Zhao X, et al. Integration of metabolomics and transcriptomics reveals major metabolic pathways and potential biomarker involved in prostate cancer. Mol Cell Proteomics. 2016;15(1):154–63. https://doi.org/10.1074/mcp.M115.052381.
83. Renz PF, Ghoshdastider U, Baghai Sain S, et al. In vivo single-cell CRISPR uncovers distinct TNF programmes in tumour evolution. Nature. 2024;632(8024):419–28. https://doi.org/10.1038/s41586-024-07663-y.
84. Rigby RJ, Carr J, Orgel K, et al. Intestinal bacteria are necessary for doxorubicin-induced intestinal damage but not for doxorubicin-induced apoptosis.

Gut Microbes. 2016;7(5):414–23. https://doi.org/10.1080/19490976.2016.1215806.
85. Sato G, Shirai Y, Namba S, et al. Pan-cancer and cross-population genome-wide association studies dissect shared genetic backgrounds underlying carcinogenesis. Nat Commun. 2023;14(1):3671. https://doi.org/10.1038/s41467-023-39136-7.
86. Shen H, Cook K, Gee HE, et al. Hypoxia, metabolism, and the circadian clock: new links to overcome radiation resistance in high-grade gliomas. J Exp Clin Cancer Res. 2020;39(1):129. https://doi.org/10.1186/s13046-020-01639-2.
87. Shree T, Haebe S, Czerwinski DK, et al. A clinical trial of therapeutic vaccination in lymphoma with serial tumor sampling and single-cell analysis. Blood Adv. 2024;8(1):130–42. https://doi.org/10.1182/bloodadvances.2023011589.
88. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49. https://doi.org/10.3322/caac.21820.
89. Sun R, Limkin EJ, Vakalopoulou M, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol. 2018;19(9):1180–91. https://doi.org/10.1016/s1470-2045(18)30413-3.
90. Tanaka A, Ogawa M, Zhou Y, et al. Proteogenomic characterization of primary colorectal cancer and metastatic progression identifies proteome-based subtypes and signatures. Cell Rep. 2024;43(2): 113810. https://doi.org/10.1016/j.celrep.2024.113810.
91. Tang C, Hobbs B, Amer A, et al. Development of an immune-pathology informed radiomics model for non-small cell lung cancer. Sci Rep. 2018;8(1):1922. https://doi.org/10.1038/s41598-018-20471-5.
92. Tirosh I, Venteicher AS, Hebert C, et al. Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. Nature 2016;309–313.https://doi.org/10.1038/nature20123.
93. Toss A, De Matteis E, Rossi E, et al. Ovarian cancer: can proteomics give new insights for therapy and diagnosis? Int J Mol Sci. 2013;14(4):8271–90. https://doi.org/10.3390/ijms14048271.
94. Velazquez-Fernandez JB, Ferreira-Souza GHM, Rodriguez-Campos J, et al. Proteomic characterization of a second-generation version of the BCGDeltaBCG1419c vaccine candidate by means of electrospray-ionization quadrupole time-of-flight mass spectrometry. Pathog Dis. 2021. https://doi.org/10.1093/femspd/ftaa070.
95. Villicana S, Castillo-Fernandez J, Hannon E, et al. Genetic impacts on DNA methylation help elucidate regulatory genomic processes. Genome Biol. 2023;24(1):176. https://doi.org/10.1186/s13059-023-03011-x.
96. Vittone J, Gill D, Goldsmith A, et al. A multi-cancer early detection blood test using machine learning detects early-stage cancers lacking USPSTF-recommended screening. NPJ Precis Oncol. 2024;8(1):91. https://doi.org/10.1038/s41698-024-00568-z.
97. Wang K, Kumar T, Wang J, et al. Archival single-cell genomics reveals persistent subclones during DCIS progression. Cell. 2023;186(18):3968-3982 e3195. https://doi.org/10.1016/j.cell.2023.07.024.
98. Werba G, Weissinger D, Kawaler EA, et al. Single-cell RNA sequencing reveals the effects of chemotherapy on human pancreatic adenocarcinoma and its tumor microenvironment. Nat Commun. 2023;14(1):797. https://doi.org/10.1038/s41467-023-36296-4.
99. Wiklund AK, Santoni G, Yan J, et al. Risk of esophageal adenocarcinoma after *Helicobacter pylori* eradication treatment in a population-based multinational cohort study. Gastroenterology. 2024;167(3):485–92. https://doi.org/10.1053/j.gastro.2024.03.016.
100. Wu MJ, Shi L, Merritt J, et al. Biology of IDH mutant cholangiocarcinoma. Hepatology. 2022;75(5):1322–37. https://doi.org/10.1002/hep.32424.
101. Wu S, Rhee KJ, Albesiano E, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 2009;15(9):1016–22. https://doi.org/10.1038/nm.2015.
102. Xiao Y, Li Y, Zhao H. Spatiotemporal metabolomic approaches to the cancer-immunity panorama: a methodological perspective. Mol Cancer. 2024;23(1):202. https://doi.org/10.1186/s12943-024-02113-9.
103. Xiao Y, Ma D, Yang YS, et al. Comprehensive metabolomics expands precision medicine for triple-negative breast cancer. Cell Res. 2022;32(5):477–90. https://doi.org/10.1038/s41422-022-00614-0.
104. Xing X, Cai L, Ouyang J, et al. Proteomics-driven noninvasive screening of circulating serum protein panels for the early diagnosis of hepatocellular carcinoma. Nat Commun. 2023;14(1):8392. https://doi.org/10.1038/s41467-023-44255-2.
105. Yang L, Li A, Wang Y, et al. Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. Signal Transduct Target Ther. 2023;8(1):35. https://doi.org/10.1038/s41392-022-01304-4.
106. Zeng Y, Jain R, Lam M, et al. DNA methylation modulated genetic variant effect on gene transcriptional regulation. Genome Biol. 2023;24(1):285. https://doi.org/10.1186/s13059-023-03130-5.
107. Zhang FL, Feng YQ, Wang JY, et al. Single cell epigenomic and transcriptomic analysis uncovers potential transcription factors regulating mitotic/meiotic switch. Cell Death Dis. 2023;14(2):134. https://doi.org/10.1038/s41419-023-05671-w.
108. Zhang L, Li Z, Skrzypczynska KM, et al. Single-Cell Analyses Inform Mechanisms of Myeloid-Targeted Therapies in Colon Cancer. Cell 2020;181(2):442–459.e429.https://doi.org/10.1016/j.cell.2020.03.048.
109. Zhang M, Bzura A, Baitei EY, et al. A gut microbiota rheostat forecasts responsiveness to PD-L1 and VEGF blockade in mesothelioma. Nat Commun. 2024;15(1):7187. https://doi.org/10.1038/s41467-024-49842-5.
110. Zhang N, Harbers L, Simonetti M, et al. High clonal diversity and spatial genetic admixture in early prostate cancer and surrounding normal tissue. Nat Commun. 2024;15(1):3475. https://doi.org/10.1038/s41467-024-47664-z.
111. Zhang N, Kandalai S, Zhou X, et al. Applying multi-omics toward tumor microbiome research. Imeta. 2023;2(1): e73. https://doi.org/10.1002/imt2.73.
112. Zhang W, Hankemeier T, Ramautar R. Next-generation capillary electrophoresis-mass spectrometry approaches in metabolomics. Curr Opin Biotechnol. 2017;43:1–7. https://doi.org/10.1016/j.copbio.2016.07.002.
113. Zhao J, Xu L, Sun J, et al. Global trends in incidence, death, burden and risk factors of early-onset cancer from 1990 to 2019. BMJ Oncol. 2023;2(1):e000049. https://doi.org/10.1136/bmjonc-2023-000049.

Publisher's Note