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MINIREVIEWS

Single-cell differential abundance detection: A new angle on dissecting tumor heterogeneity

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Abstract

Tumor heterogeneity is one of the central challenges in oncology, contributing to treatment resistance and disease recurrence. Bulk RNA sequencing has advanced understanding of tumor biology, yet its averaging effect conceals cell type-specific alterations. Single-cell RNA sequencing overcomes this limitation by capturing gene expression and cellular phenotypes with high-resolution, thereby illuminating tumor composition and the surrounding microenvironment. Within this framework, differential abundance (DA) detection has emerged as a powerful strategy to quantify shifts in cell population proportions across conditions. Unlike differential gene expression, DA highlights compositional changes in cellular ecosystems, offering a structural perspective on tumor dynamics. This review introduces the main categories of DA methods in single-cell RNA sequencing analysis, outlining their modeling strategies, assumptions, and representative applications in oncology. We also discuss key challenges, including reliance on clustering quality and batch correction. By linking methodological principles with biological insight, this review clarifies the role of DA detection in single-cell oncology and provides a conceptual framework for integrating compositional analysis into efforts to understand tumor evolution, treatment response, and disease stratification.

Key Words: Single-cell RNA sequencing; Tumor heterogeneity; Differential abundance detection; Tumor microenvironment; Precision oncology; Immune remodeling; Cellular composition

Core Tip: This review highlights differential abundance (DA) detection as a transformative framework in single-cell oncology, enabling high-resolution deconstruction of tumor heterogeneity. It surveys widely adopted DA methods and demonstrates how capturing dynamic shifts in cellular ecosystems yields critical mechanistic insights, supports clinical decision-making, and informs precision therapeutic strategies. The ongoing methodological refinements and multi-omics convergence will further elevate DA detection to a cornerstone technology in precision oncology.

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INTRODUCTION

Tumor heterogeneity remains one of the most formidable barriers in oncology, continuing to drive variability in disease progression, therapeutic response, and clinical outcomes despite major therapeutic advances[1,2]. To address this challenge, a deeper understanding of the hierarchical organization of tumors is essential - not only helps clarify the fundamental principles of tumor evolution but also provides a theoretical foundation for identifying new therapeutic targets and refining intervention strategies, ultimately aiming to improve treatment efficacy and patient survival[3,4]. Early studies on tumor heterogeneity largely relied on bulk RNA sequencing. Although this approach captures extensive transcriptomic information, it measures only average signals across cell populations. As a result, it lacks the resolution to detect transcriptional heterogeneity at the single-cell level, limiting its ability to dissect the complex cellular composition and dynamic reorganization within tumor tissues[5].

The advent of single-cell RNA sequencing (scRNA-seq) has propelled cancer research from tissue-level profiling to a high-resolution, single-cell paradigm[5,6]. Compared to conventional approaches, scRNA-seq has deepened our understanding of tumor lineage diversity and the intricacies of the immune microenvironment[7,8]. It has also reshaped prevailing concepts of tumor initiation and progression, laying a robust foundation for precision oncology[9]. Most applications, however, have focused on differentially expressed genes (DEGs) to uncover regulatory mechanisms and therapeutic targets[10,11]. Yet many clinically relevant features are not solely reflected in transcriptional shifts but also in cellular composition changes within the tumor environment[12-14]. During tumor progression, therapy, or immune responses, alterations in the abundance or proportion of specific subpopulations often provide more immediate functional and prognostic signals[15,16]. In this context, single-cell differential abundance (DA) detection, provides exactly such a solution by statistically detecting changes in cell-type or state frequencies across conditions, thereby offering a compositional perspective distinct from gene-centric DEG analysis[17,18].

Initially applied in microbiome studies[19,20], DA concepts were later adapted to single-cell omics data. Some studies reported differences in cell-type composition across conditions, but often without measures of statistical uncertainty[21,22]. These pioneering studies laid the foundation for subsequent single-cell-specific DA methods. Early implementations of DA detection typically relied on conventional statistical tests, such as Student's *t*-test or Wilcoxon test, to compare changes in cell type abundance[23]. Since 2018, an increasing number of DA methods specifically tailored for single-cell data have been developed. Many of these methods incorporate covariate adjustment strategies. This enhances statistical power and improves sensitivity in detecting shifts in rare or functionally critical cell populations[17,24,25]. Together, DA detection represents a paradigm shift from a gene-centric to a cell-composition-centric view of tumor heterogeneity. It bridges molecular mechanisms with microecological dynamics and links molecular-level insights to clinically relevant phenotypes.

In this review, we provide a comprehensive overview of the theoretical foundations and representative methodologies of DA detection, outline a standardized analytical workflow, and highlight its critical applications in the study of tumor heterogeneity. Furthermore, we discuss the current technical challenges and propose future directions for methodological development.

THE PROCESSES OF DA DETECTION

As a powerful complement to traditional analysis of DEGs, DA detection offers a novel framework for interrogating the dynamic reorganization of cellular architecture, thereby enhancing our understanding of tumor heterogeneity. While DEGs analysis has long been a mainstay in transcriptomics studies, it cannot account for shifts in cell-type proportions that may carry important biological meaning - especially in heterogeneous environments like tumors. As a result, there is growing interest in establishing clear, standardized pipelines for DA detection to ensure results are both reproducible and biologically interpretable. A complete DA detection typically follows four main steps: Data preprocessing, selection of analytical strategies, cell-type annotation, and statistical testing (Figure 1A). These steps are briefly outlined below.

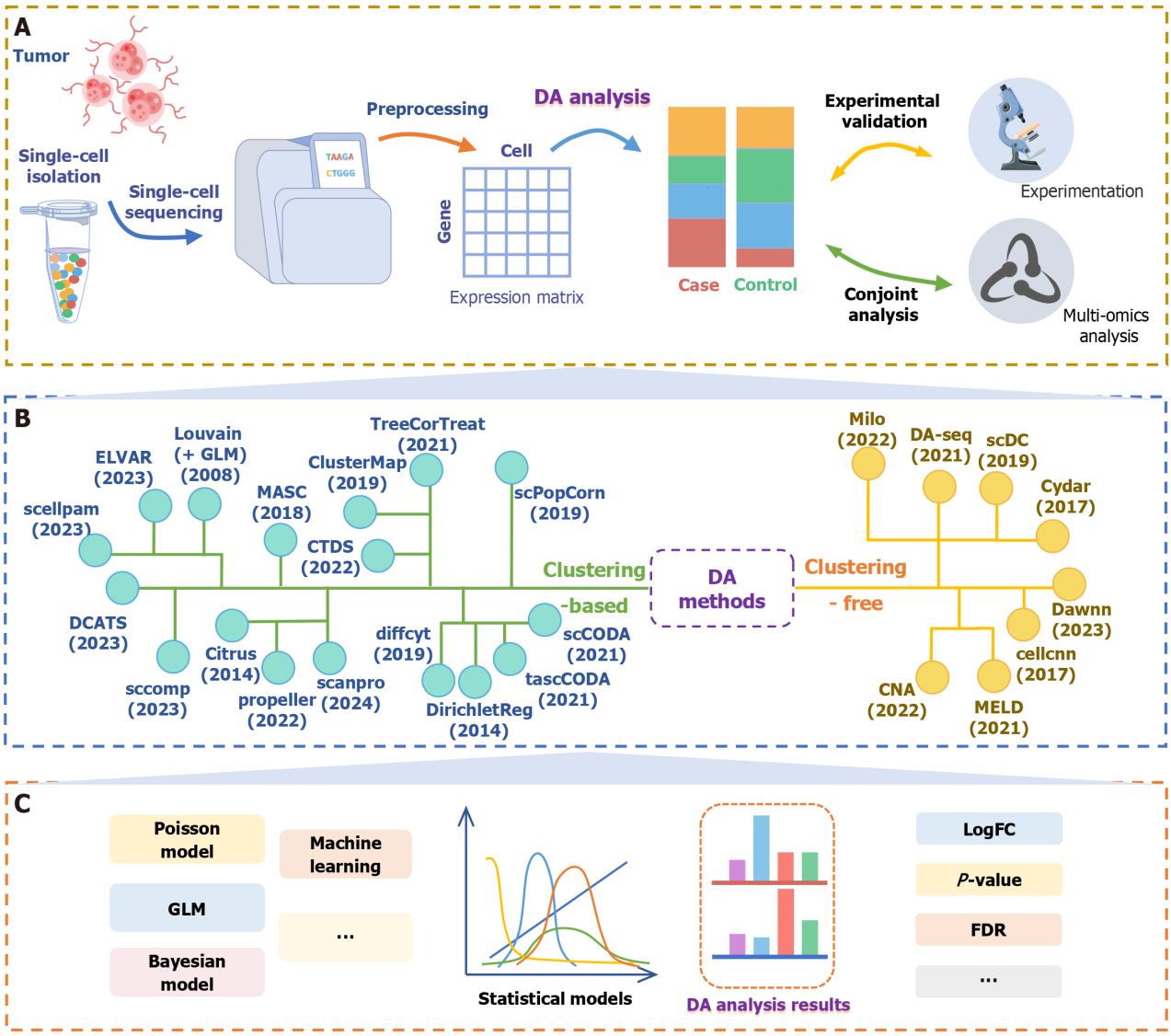

Figure 1 Overview of single-cell differential abundance detection. A: The general workflow of single-cell differential abundance (DA) analysis. Data obtained from single-cell sequencing are preprocessed and then subjected to DA detection. The results of DA detection are often validated experimentally or integrated with multi-omics data to facilitate deeper insights into the dataset; B: Single-cell DA methods can be broadly categorized based on whether they rely on clustering strategies; C: Common statistical models and typical output metrics used in single-cell DA detection. DA: Differential abundance; GLM: Generalized linear models; logFC: Log2 fold change; FDR: False discovery rate.

Data preprocessing

Before DA detection, scRNA-seq data must undergo rigorous quality control and normalization, following standard protocols in single-cell transcriptomics. Common preprocessing steps include filtering out low-quality cells (*e.g.*, those with excessive mitochondrial gene content), removing genes that are rarely expressed, and performing data normalization. These steps reduce biases and ensure that the abundance estimates in later stages reflect true biological variation rather than technical artifacts.

Choice of analytical strategy

Approaches to DA detection can be categorized into two main classes: Clustering-based and clustering-free ones (Figure 1B). More detailed descriptions of these methods regarding their principles, algorithms, code availability, *etc.* have been placed in Zenodo (https://zenodo.org/records/17113256). Clustering-based methods rely on cell groups identified through unsupervised clustering (such as Leiden or Louvain algorithms). Once clusters are defined, the relative abundance of each cluster can be compared across diverse conditions[26,27]. Clustering-based approaches work well when cell types are clearly separated and can be reliably annotated. Bioinformatics methods in this category include scCODA[28], propeller[29], and sccomp[26], which have been applied in various biological contexts. Clustering-free methods take a different route. Instead of relying on predefined clusters, they examine the local neighborhood structure of cells within a reduced dimensionality space[24,25,30]. These methods are especially useful when cell states transition gradually or when cell boundaries are hard to define. By focusing on spatial or topological relationships among cells, clustering-free tools like Milo and DA-seq can detect more subtle changes in cell populations that might be missed by

clustering-based techniques[24,25].

Cell annotation

Accurate annotation of cell types or states is essential for interpreting the DA results. In clustering-based workflows, cell annotations serve as the basis for abundance comparison. Even in clustering-free approaches, marker gene-based interpretation is typically required after regions of DA are identified. Poor or overly coarse annotations can obscure subtle but functionally relevant shifts in cellular composition, and therefore integrating high-quality reference markers or leveraging supervised annotation tools is strongly recommended.

Statistical modeling and significance evaluation

The final step involves selecting appropriate statistical models to test for differences in cell-type abundance. The choice of model should consider sample size, data complexity, and the presence of covariates (Figure 1C). For clinical datasets with complex covariates, such as sex, treatment regimen, or age, models based on generalized linear mixed models or Bayesian regression frameworks (*e.g.*, scCODA, scDC, Milo) are recommended[24,28,31]. These approaches allow for the flexible incorporation of covariates, enabling researchers to control for potential confounding factors and improve the robustness of statistical inference. In small-sample contexts, resampling-based strategies such as that used by propeller help stabilize estimates and improve robustness by averaging over multiple permutations or subsamples[29]. As shown in Figure 1C, key outputs from DA analyses typically include $\log_2$ fold change, adjusted *P* value, and false discovery rate. Importantly, statistical significance alone does not guarantee biological relevance. Researchers are encouraged to validate DA findings through complementary approaches, such as flow cytometry or spatial transcriptomics, to confirm changes in cell abundance.

DA DETECTION IN INVESTIGATING TUMOR HETEROGENEITY

By quantitatively comparing changes in the abundance of cell populations across distinct physiological and pathological states, DA detection not only enhances sensitivity in detecting cellular structural remodeling but also serves as a critical bridge linking molecular mechanisms to clinical phenotypes. In doing so, DA detection is driving a conceptual shift in tumor heterogeneity research from a gene-centric, static perspective to a systems-level ecological framework that emphasizes the dynamic nature of cellular organization. To comprehensively assess the research potential and translational value of DA detection in oncology, this review focuses on three major dimensions: Mechanistic insight, clinical decision support, and precision therapy (Figure 2). To illustrate the practical use of DA detection in oncology, Table 1 compiles representative tumor-specific applications. For each cancer type, we included 1-2 studies in which DA methods were explicitly applied, prioritizing examples that yielded biological or clinical insights. The purpose is to highlight the breadth of DA applications across diverse tumor contexts, rather than to provide an exhaustive or comparative evaluation of all available studies.

DA DETECTION ENABLES MECHANISTIC INSIGHTS INTO TUMOR HETEROGENEITY

The initiation, progression, and treatment response of tumors are accompanied by extensive remodeling of the immune landscape and broader cellular ecosystem. DA detection provides a robust framework for quantifying changes in the abundance of specific cell types or subpopulations, thereby uncovering biological mechanisms that are often inaccessible through gene expression analyses alone. By revealing how cellular ecosystems are reshaped over time or under perturbation, DA detection offers unique mechanistic insights into the dynamic nature of tumor heterogeneity (Figure 2A).

A compelling example of this is found in high-grade serous ovarian cancer, where Launonen *et al*[32] use DA detection to investigate how chemotherapy reshapes the immune landscapes. Their results revealed the novel macrophage subsets and altered states of cluster of differentiation (CD) 8+ and CD4+ T cells following treatment, suggesting a reconfiguration of immune functionality rather than a simple depletion of immune components. Notably, most differentially abundant epithelial cell states were detected in untreated tumors, suggesting that chemotherapy reduces not only tumor burden but also phenotypic diversity. Further spatial analysis indicated chemotherapy redirected CD8+ T cell interactions from tumor cells toward macrophages, hinting at an adaptive reorganization of cell-cell communication networks[32].

The utility of DA detection in revealing lineage bias was further demonstrated in a study by Garner *et al*[33] who examined hematopoietic dynamics in breast cancer. They found that tumor-bearing mice exhibited a skewing of hematopoiesis toward the myeloid lineage, with a marked reduction in erythroid and lymphoid progenitors. This observation supported the hypothesis that solid tumors can influence systemic immunity by reprogramming bone marrow output - a phenomenon with far-reaching implications for immunosuppression and metastasis[33].

In addition to treatment-related changes, DA detection is also well suited for tracking early events during tumor progression. For instance, Gan *et al*[34] used DA detection to trace immune remodeling across sequential pathological stages. As tissue progressed from the transition from non-atrophic gastritis to intestinal metaplasia and ultimately carcinoma, the proportion of immune cells steadily increased, while epithelial components declined. This compositional shift highlighted the intestinal metaplasia stage as a potential window of immune escape. Further analysis of changes in immune cell abundance identified the interleukin-17 signaling pathway as a key regulatory factor in this process, offering

Table 1 Some specific applications of differential abundance methods in the study of tumor heterogeneity

Tumor type	Practical application	DA method	Ref.
Head and neck squamous cell carcinoma	Milo identified FRC-like fibroblasts as significantly enriched in immune-hot HNSCC tumors, correlating with better immunotherapy response	Milo	[44]
Gastric cancer	The DA method revealed increasing immune cell abundance (T cell, B cell, NK cell) from non-atrophic gastritis to gastric cancer, with intestinal metaplasia as the key immune evasion turning point	Milo	[34]
Colorectal cancer	DA analysis showed BRAFi + EGFRi enriched EECs in $BRAF^{V600E}$ CRC, while LSD1 inhibition blocked this and enhanced efficacy	propeller	[38]
High-grade serous ovarian cancer	DA analysis revealed myeloid-driven CD8+ T cell exhaustion in ovarian cancer post-chemotherapy, highlighting NECTIN2-TIGIT as an immunotherapy target	propeller	[32]
Pancreatic cancer	DA analysis revealed that neoadjuvant therapy reshapes the pancreatic cancer TME, causing significant shifts in specific immune and fibroblast subpopulations	scCODA	[45]
Lung cancer	Cydar revealed that lung cancers with different driver mutations exhibit significant shifts in T cell subsets, shaping distinct differentiation patterns. Additionally, diffcyt linked specific CAF phenotypes (ifnCAFs, iCAFs) to good prognosis and others (tCAFs, hypoxic tCAFs) to poor prognosis	Cydar/diffcyt	[46,47]
Clear cell renal cell carcinoma	DA analysis showed high-risk ccRCC patients had protumor immune phenotypes lacking specific immune checkpoints	propeller	[48]
Melanoma	The propeller showed immune "cold" uveal melanoma had depleted immune cell subsets, while "hot" cases were enriched with immune response-related cells. Additionally, Milo revealed significant enrichment of antitumor immune cells after personalized neoantigen vaccination in melanoma patients	propeller/Milo	[49,50]
Multiple myeloma	DA-seq showed that post-BCMA CAR-T therapy, responders enriched effector immune cells, while non-responders enriched immunosuppressive subsets. The propeller used DA to compare immune cells in long-term multiple myeloma survivors and controls, finding significant lasting changes decades after treatment	DA-seq/propeller	[51,52]
B cell lymphoma	scCODA showed responders to CAR-T therapy had significant enrichment of antitumor immune cell subsets. Cydar revealed regulatory CAR-T cells enriched in resistant patients after CD19-CAR-T therapy, linked to treatment resistance	scCODA/Cydar	[53,54]
Acute myeloid leukemia	DA analysis revealed significant myeloid and immune cell changes in STAG2-mutant AML, linked to disease and gene abnormalities	Cydar	[55]
Pediatric Hodgkin lymphoma	DA analysis showed multiple T cell subsets were reduced in pediatric Hodgkin lymphoma tumors, indicating widespread T cell suppression	DCATS	[56]

FRC: Fibroblastic reticular cell; HNSCC: Head and neck squamous cell carcinoma; DA: Differential abundance; BRAFi: V-raf murine sarcoma viral oncogene homolog B inhibitor; EGFRi: Epidermal growth factor receptor inhibition; EECs: Enteroendocrine cells; $BRAF^{V600E}$: V-raf murine sarcoma viral oncogene homolog B (V600E); CRC: Colorectal cancer; LSD1: Lysine-specific demethylase 1; CD: Cluster of differentiation; NECTIN2: Nectin cell adhesion molecule 2; TIGIT: T-cell immunoglobulin and ITIM domain; TME: Tumor microenvironment; CAF: Cancer-associated fibroblast; ifnCAF: Interferon-responsive-cancer-associated fibroblast; iCAF: Inflammatory cancer-associated fibroblast; tCAF: Tumor-associated fibroblast; ccRCC: Clear cell renal cell carcinoma; BCMA: B-cell maturation antigen; CAR-T: Chimeric antigen receptor T-cell; AML: Acute myeloid leukemia.

a potential new target for early diagnosis and therapeutic intervention in gastric cancer[34].

DA DETECTION PROVIDES INSIGHTS FOR CLINICAL DECISION-MAKING

The mechanistic insights offered by DA detection naturally extend to the clinical realm, where tumor heterogeneity often manifests as variability in treatment response, disease progression, and therapeutic resistance. By quantitatively profiling changes in cell-type composition across patients or timepoints, DA detection offers complementary information that can help interpret clinically relevant outcomes and generate hypotheses for patient stratification (Figure 2B).

A notable example comes from a study of locally advanced rectal cancer, in which patients received short-course radiotherapy combined with neoadjuvant immunochemotherapy. DA detection revealed a marked increase in monocytes, CD8+ T cells, and plasma cells post-treatment, alongside a decrease in B cells, macrophages, neutrophils, T helper 17, and regulatory T cells[35]. Crucially, integrated analysis identified a triggering receptor expressed on myeloid

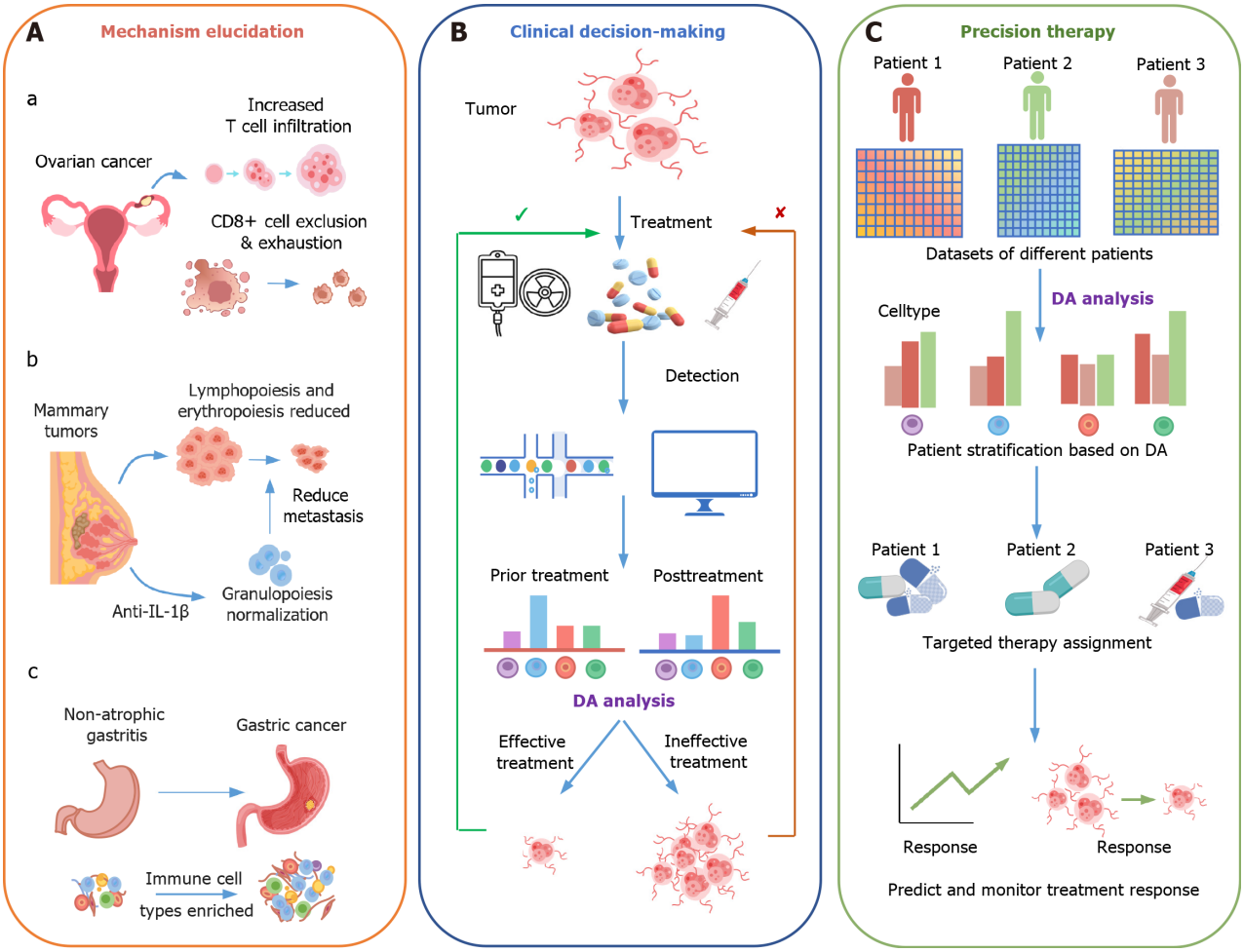

Figure 2 Three representative applications of differential abundance detection in tumor heterogeneity research. A: Examples illustrating how differential abundance (DA) detection facilitates elucidation of mechanisms underlying tumor heterogeneity, ovarian cancer (a), mammary tumors (b), gastric cancer (c). By revealing changes in cellular composition, DA detection aids in the interpretation of tumor biology and resistance mechanisms; B: The role of DA detection in clinical decision-making. By comparing cell-type abundances before and after treatment, DA detection enables evaluation of therapeutic efficacy, helping clinicians to adjust treatment strategies promptly; C: The contribution of DA detection to advancing precision medicine. By performing individualized DA detection across patients with the same disease, DA detection supports personalized drug selection and continuously refines therapeutic outcomes, thereby promoting the development of precision therapy. IL: Interleukin; CD: Cluster of differentiation; DA: Differential abundance.

cells 1+ pro-inflammatory monocyte/macrophage subset whose expansion correlated with a favorable response. This suggests that DA-derived biomarkers can capture therapy-induced remodeling of the tumor immune microenvironment, a feature often missed by conventional molecular markers. When combined with existing modalities like magnetic resonance imaging-based magnetic resonance tumor regression grade, DA markers could significantly improve predictive accuracy, guiding more personalized treatment strategies[35].

Beyond response, DA detection identifies features associated with prognosis. In a comparison of primary gastric cancer and its peritoneal metastases, Li *et al*[36] uncovered a dramatic shift in cancer-associated fibroblast (CAF) populations. Metastatic lesions were depleted of inflammatory CAFs but enriched in matrix cancer-associated fibroblasts, a shift linked to immune suppression and therapeutic resistance. This DA-based stratification pinpoints high-risk patients who might benefit from aggressive or novel therapies targeting the metastatic CAF niche, complementing traditional markers that may be uninformative in this context[36].

Overall, these examples highlight that DA detection provides valuable, clinically relevant insights into therapy response and prognosis. While DA-derived biomarkers cannot replace established molecular markers, they offer complementary information that can refine patient stratification, support treatment decision-making, and enhance the predictive power of existing modalities when integrated into multi-dimensional clinical assessment.

DA DETECTION SUPPORTS THE DEVELOPMENT OF PRECISION TREATMENT

As cancer treatment continues to move toward personalized and mechanism-guided strategies, understanding how the tumor microenvironment adapts under therapeutic pressure has become increasingly important. DA detection offers a practical and scalable approach for identifying treatment-induced changes in cellular composition, revealing drug-

resistant subpopulations, and evaluating the efficacy of combination therapies (Figure 2C).

In the context of immunotherapy, DA detection has been instrumental in elucidating immune cell dynamics under dual checkpoint blockade. In a study investigating combination immunotherapy in melanoma, Andrews *et al*[37] applied the Milo to perform DA detection on CD8+ T cells from a mouse model, and the results revealed that programmed death-1 deficient and lymphocyte activation gene 3 deficient CD8+ T cells were transcriptionally distinct, characterized by broad T cell receptor clonality and enrichment of effector-like and interferon-responsive genes. These populations displayed enhanced effector function, including interferon-γ release, providing mechanistic support for the combined blockade of programmed death-1 and lymphocyte activation gene 3 as a therapeutic strategy.

DA detection has also played a crucial role in elucidating mechanisms of immune exhaustion under therapeutic pressure. Using DA detection, Launonen *et al*[32] found that chemotherapy induced spatially confined exhaustion of CD8+ T cells, mediated through the nectin cell adhesion molecule 2-T-cell immunoglobulin and ITIM domain axis. Based on these findings, they proposed a precision immunotherapy strategy tailored to immune checkpoint blockade. Furthermore, Ladaika *et al*[38] combined single-cell data with DA detection to examine v-raf murine sarcoma viral oncogene homolog B and epidermal growth factor receptor inhibition in v-raf murine sarcoma viral oncogene homolog B (V600E) mutation-mutant colorectal cancer. They observed consistent enrichment of enteroendocrine cells across preclinical models and clinical specimens following treatment. This variation in epithelial lineage composition pointed to adaptive resistance *via* cell fate reprogramming and informed the proposal of a novel therapeutic combination designed to constrain lineage plasticity. Briefly, DA detection has become a crucial tool for deciphering treatment resistance and optimizing combination strategies. By uncovering the evolutionary dynamics of cell populations under drug pressure, it offers a new perspective for targeted therapies[39,40].

LIMITATIONS OF DA DETECTION IN ELUCIDATING TUMOR HETEROGENEITY

Despite its growing utility, DA detection faces several technical and conceptual challenges that may limit its interpretability and clinical applicability. First of all, the limited interpretability remains a major bottleneck across current DA methods. Many DA methods rely on embeddings, gene-based structures, or Bayesian modeling frameworks to detect compositional changes[31,41]. While these techniques enhance sensitivity, they often generate abstract outputs - such as altered "cellular neighborhoods" or latent cell regions rather than clearly annotated cell types. This ambiguity complicates downstream biological interpretation, especially for users without computational experience[24,42]. Moreover, DA detection results are typically reported as statistical metrics (*e.g.*, $\log_2$ fold change and adjusted *P*-value), lacking direct linkage to known functional pathways or phenotypic characteristics[42].

A second major issue concerns annotation dependency. Clustering-based methods generally require well-defined and high-resolution cell-type labels as the basis for abundance comparison. Even clustering-free methods often require *post hoc* interpretation using marker genes or reference atlases. Inaccurate or incomplete annotation can obscure biological meaningful shifts, particularly for rare, intermediate, or novel cell subpopulations. Thus, improving cell-type identification remains essential to enhance the robustness of DA findings.

Moreover, trade-offs between statistical power and computational burden present practical limitations[43]. In small-sample or low-abundance scenarios, some methods often suffer from low sensitivity, while others attempt to compensate through resampling, subsampling or complex modeling strategies that may increase false negatives or reduce scalability [29]. Tools incorporating multiple covariates or Bayesian inference (*e.g.*, Milo and scCODA) often require considerable computational resources, making them difficult to apply to large-scale diverse clinical cohorts[24,28].

In summary, although DA detection provides a powerful tool for deciphering tumor heterogeneity dynamics, its widespread adoption still requires further methodological innovation to improve the interpretability, flexibility, and scalability - particularly in translational and clinical contexts. Addressing these challenges, emerging methodological advances offer promising avenues for improvement. For example, integration with spatial transcriptomics or multi-omics datasets can link cell composition changes to spatial context or complementary molecular layers, potentially enhancing interpretability, supporting more accurate annotation, and improving clinical relevance, thereby facilitating broader adoption of DA detection in translational oncology.

CONCLUSION

DA detection has emerged as a conceptual and methodological advance in single-cell data analysis, offering a powerful framework to propel a paradigm shift in tumor heterogeneity research - from a static, gene-centric view focused on differential gene expression toward the dynamics centered on the ecological structure of cell populations. By accurately identifying key cell types or subpopulations whose abundances change significantly across physiological or pathological states, DA detection not only deepens our understanding of the evolving tumor immune microenvironment but also demonstrates broad translational potential in early disease detection, therapeutic response assessment, and personalized intervention strategies.

Compared to traditional approaches, DA detection has several advantages. It is particularly effective at capturing dynamic microenvironmental remodeling, detecting lineage bias, and uncovering cellular correlates of treatment response. In addition, many DA tools incorporate covariate modeling, enabling adjustment for patient-specific factors such as age, treatment, or sampling batch - an important consideration for clinical translation. However, its adoption in translational oncology remains limited by methodological challenges, including dependency on accurate annotation,

limited interpretability of complex models, and the computational burden of scaling to large cohorts.

Looking forward, DA detection is expected to evolve across several critical dimensions. First, multi-modal integration represents a major breakthrough opportunity. The fusion of DA detection with spatial transcriptomics, single-cell assay for transposase-accessible chromatin using sequencing, and proteomics will enable high-resolution dissection of tumor cell heterogeneity and evolutionary trajectories. Second, emerging artificial intelligence algorithms, such as graph neural networks and deep generative models, are likely to be increasingly incorporated into DA frameworks, enhancing the modeling of cellular neighborhood relationships and improving both analytical sensitivity and generalizability. In parallel, the development of high-quality, well-annotated single-cell tumor atlases will be essential for establishing DA detection as a core tool within precision medicine, especially in constructing interpretable links between cellular composition, clinical phenotypes, and treatment outcomes.

FOOTNOTES

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