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Single-Cell Immunology and Multi-Omics: Recent Advances and Emerging Applications in Precision Medicine

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Abstract: The rapid advancement of single-cell sequencing technologies has revolutionized immunological research by enabling comprehensive characterization of immune cells at single-cell resolution. Conventional bulk analytical methods often fail to capture cellular heterogeneity, limiting the understanding of immune mechanisms underlying cancer, autoimmune diseases, infectious disorders, and neurodegenerative conditions. The integration of multi-omics technologies offers new opportunities to overcome these limitations and accelerate precision medicine. **Objective:** This review aims to synthesize recent advances in single-cell immunology and multi-omics, evaluate their applications across major immunological fields, and identify emerging opportunities and challenges for clinical translation. **Methodology:** This study employed a qualitative narrative literature review using a structured literature search. Scientific publications were retrieved from PubMed, PubMed Central, Google Scholar, and bioRxiv. Eligible studies were selected based on predefined inclusion criteria and analyzed using thematic narrative synthesis to identify technological developments, translational applications, methodological challenges, and future research directions. **Findings:** The review demonstrates that single-cell RNA sequencing, CITE-seq, spatial transcriptomics, and integrated multi-omics have substantially improved the identification of immune cell heterogeneity, cellular communication, and disease-specific molecular mechanisms. These technologies have advanced immune atlas construction, enhanced understanding of tumor immune microenvironments, improved characterization of autoimmune diseases, and revealed novel neuroimmune interactions. Artificial intelligence and computational biology further strengthen data integration and biological interpretation. **Implications:** The findings support the application of single-cell multi-omics in biomarker discovery, disease stratification, therapeutic target identification, and personalized treatment strategies while highlighting the need for standardized analytical pipelines and clinical validation. **Originality:** This review provides an integrated synthesis of technological innovation, computational methodologies, immune atlas research, oncology, autoimmune diseases, and neuroimmunology within a unified precision immunology framework, offering a comprehensive perspective that extends beyond previous technology- or disease-specific reviews.

Keywords: single-cell immunology; multi-omics; scRNA-seq; spatial transcriptomics; precision medicine.

INTRODUCTION

The human immune system consists of a highly diverse network of innate and adaptive immune cells that interact continuously to maintain tissue homeostasis, eliminate pathogens, and regulate inflammatory responses. Immune cell populations are not uniform; even cells within the same phenotypic subset may display distinct transcriptional, epigenetic, metabolic, and functional states. This complexity is clinically important because immune dysregulation contributes to cancer, autoimmune disorders, chronic inflammatory diseases, infectious diseases, and neurodegenerative conditions. Conventional approaches such as flow cytometry, western blotting, and bulk RNA sequencing have advanced immunological research, but they generate averaged molecular signals from mixed cell populations. As a result, rare immune subsets and transient cellular states that may determine disease progression or therapeutic response are often overlooked. The growth of precision medicine has therefore created an urgent need for technologies capable of characterizing immune cells at single-cell resolution.

The emergence of single-cell RNA sequencing (scRNA-seq) has transformed the study of immune heterogeneity by enabling genome-wide transcriptomic profiling at the level of individual cells. This development has been expanded through single-cell multi-omics platforms that integrate transcriptomic, proteomic, epigenomic, and spatial information within the same biological context. Baysoy describe how single-cell multi-omics has moved beyond transcriptomics alone toward integrated molecular profiling (Baysoy et al., 2023). CITE-seq has further strengthened this development by combining gene expression analysis with surface protein measurement, allowing immune cells to be interpreted using both transcriptomic signatures and classical immunophenotyping markers (Song et al., 2025). In parallel, computational approaches have become increasingly important for integrating complex single-cell datasets. Schäfer emphasize the need to combine single-cell data with prior biological knowledge (Schäfer et al., 2024), while Yiu highlight the growing role of foundation models and artificial intelligence in cell annotation, trajectory inference, and multimodal data integration (Yiu et al., 2025).

A second body of literature has applied single-cell technologies to construct immune cell atlases across human development, aging, and hematopoiesis. Xuan developed an immunophenotype-coupled transcriptomic atlas of human hematopoietic progenitors, providing a reference for understanding immune cell development from bone marrow populations (Xuan et al., 2024). Haniffa showed how single-cell multi-omics can decode the human prenatal immune system and reveal early immune developmental trajectories (Haniffa et al., 2025). Gong extended this atlas-based approach by profiling age-related immune dynamics in healthy adults (Gong et al., 2025). Similarly, Daniel demonstrated that multimodal classification frameworks can improve immune cell annotation across lineages and tissues (Daniel et al., 2025). These studies have created valuable reference maps, but they are often discussed separately from disease-specific and translational applications.

A third group of studies has focused on disease-specific applications of single-cell immunology, especially in cancer, autoimmune diseases, and neuroimmunology. In tumor immunology, single-cell RNA sequencing has revealed the diversity and functional states of immune cells within the tumor microenvironment (Ma et al., 2025). Spatial transcriptomic approaches further demonstrate that immune responses are shaped not only by cell identity but also by tissue localization and cellular communication (Zheng et al., 2025). In autoimmune disease, multi-omics approaches have supported biomarker discovery and improved understanding of disease-specific immune dysregulation (Zhang et al., 2025). Feng showed that spatial transcriptomic profiling can define pathogenic inflammatory niches in chronic active multiple sclerosis lesions (Feng et al., 2025). In neuroimmunology, integrated single-cell multi-omics has begun to reveal immune interactions associated with neurodegenerative disease, including Alzheimer's disease (Zhao et al., 2026). Although these studies demonstrate major progress, existing reviews often focus on one disease area or one technological platform, leaving a need for an integrated synthesis across methodological, atlas-based, and disease-oriented developments.

Therefore, this review aims to synthesize recent advances in single-cell immunology and multi-omics by integrating evidence from studies on technological innovation, computational methodology, immune atlas construction, tumor immunology, autoimmune diseases, and neuroimmunology. This review does not merely summarize individual studies, but critically examines how these technologies complement one another, what methodological limitations remain, and how single-cell multi-omics may support biomarker discovery, disease stratification, and precision immunology.

This review argues that the convergence of single-cell sequencing, spatial multi-omics, artificial intelligence, and systems immunology has shifted immunological research from descriptive cell profiling toward mechanistic and clinically actionable immune characterization. By integrating multiple molecular layers at single-cell resolution, researchers can identify immune heterogeneity, cellular interactions, regulatory networks, and disease-specific biomarkers more accurately than with conventional bulk approaches.

Therefore, standardized computational pipelines, validated biomarkers, and clinically applicable multi-omics platforms are essential for translating single-cell immunology into next-generation precision medicine.

RESEARCH METHOD

The unit of analysis in this study consisted of published scientific literature addressing the application of single-cell immunology and multi-omics technologies in immunological research. The review focused on peer-reviewed articles discussing methodological developments, computational approaches, immune cell atlas construction, tumor immunology, autoimmune diseases, and neuroimmunology. Individual publications served as the primary analytical units, while the scientific evidence, methodological characteristics, technological innovations, and biological findings reported in each study constituted the principal objects of analysis.

This study employed a qualitative narrative literature review with a structured literature search approach. A narrative review was selected because it allows comprehensive synthesis and critical interpretation of evidence originating from diverse study designs, including original research articles, methodological papers, review articles, and translational studies. Unlike systematic reviews that primarily evaluate intervention effectiveness, the present review aimed to integrate current knowledge across multiple domains of single-cell immunology, identify emerging scientific trends, discuss methodological advances, and highlight future opportunities for clinical translation. This approach was considered appropriate because the field is rapidly evolving and encompasses heterogeneous technologies, analytical platforms, and biomedical applications.

Scientific publications were retrieved from four major electronic databases, namely PubMed, PubMed Central (PMC), Google Scholar, and bioRxiv. The literature search focused on studies published between January 2024 and June 2025, while several landmark methodological references published before 2024 were included to provide essential conceptual and technological background where necessary. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords, including *"single-cell immunology"*, *"scRNA-seq"*, *"single-cell multi-omics"*, *"CITE-seq"*, *"spatial transcriptomics"*, *"immune cells"*, *"tumor microenvironment"*, *"autoimmune disease"*, and *"neuroimmunology"*. Only articles published in English and available in full text were considered eligible.

The literature collection process was conducted through several sequential stages. First, potentially relevant publications were identified through database searching using predefined search terms. Second, duplicate records and studies unrelated to immunology or single-cell multi-omics were excluded. Third, titles and abstracts were screened according to predefined inclusion criteria, followed by full-text assessment of eligible articles. Studies were included if they discussed methodological developments, biological discoveries, computational approaches, or clinical applications of single-cell immunology and multi-omics technologies. Articles lacking sufficient methodological information, conference abstracts without full manuscripts, editorials without substantial scientific discussion, and publications outside the review scope were excluded. Following the selection process, twenty highly relevant publications were retained for qualitative synthesis.

Data were analyzed using thematic narrative synthesis. Information extracted from each study included publication characteristics, study objectives, single-cell technologies employed, computational methods, disease focus, principal findings, methodological strengths, and reported limitations. The extracted evidence was subsequently organized into five thematic categories: (1) technological and methodological foundations, (2) human immune cell atlases, (3) tumor immune microenvironment, (4) autoimmune diseases, and (5) neuroimmunology. Comparative analysis was then performed to identify recurring scientific patterns, methodological advances, remaining knowledge gaps, and future research directions. This analytical approach enabled a critical integration of recent evidence while providing a comprehensive overview of the evolving role of single-cell multi-omics in advancing immunological research and precision medicine.

RESULT

Technological and Methodological Foundations

The reviewed literature shows that single-cell multi-omics has developed from transcriptome-based profiling into an integrated analytical platform capable of capturing multiple molecular layers within individual cells. Single-cell RNA sequencing remains the foundation of this field because it enables genome-wide measurement of transcriptional activity at single-cell resolution. However, recent developments have expanded this approach by incorporating protein expression, chromatin accessibility, spatial localization, and computational modeling. These advances allow researchers to define immune cell identity, functional states, lineage relationships, and tissue-specific organization more accurately than conventional bulk approaches.

CITE-seq represents one of the most important methodological advances in single-cell immunology. By combining transcriptomic data with surface protein quantification using antibody-derived tags, CITE-seq bridges the gap between molecular sequencing and classical immune phenotyping. This is particularly important in immunology because many immune cell subsets are traditionally defined by surface markers. In addition, artificial intelligence and foundation models have become increasingly important for analyzing large-scale single-cell datasets. These computational approaches support cell annotation, trajectory inference, multimodal data integration, and prediction of cellular responses. Overall, technological and computational advances have shifted single-cell immunology from descriptive cell classification toward integrated and mechanistic immune profiling.

Human Immune Cell Atlases

The synthesis also identified immune atlas construction as a major application of single-cell multi-omics. Human immune atlases provide reference maps for understanding immune development, immune aging, hematopoiesis, and tissue-specific immune organization. Studies on the human prenatal immune system show that single-cell and spatial genomics can reveal the timing, sequence, and tissue microenvironments involved in early immune cell development. These findings are important for understanding congenital immune disorders and the long-term consequences of early immune programming.

In adult populations, longitudinal multi-omic profiling has provided insight into age-related immune dynamics. The Human Immune Health Atlas demonstrated that immune composition and transcriptional states change across the lifespan and in response to antigenic stimulation. In particular, age-related transcriptional reprogramming of T cell subsets suggests that immune aging involves intrinsic cellular programs rather than only systemic inflammation. CITE-seq-based profiling of hematopoietic progenitors further identified diverse stem cell, progenitor, immune, stromal, and transitional populations in human bone marrow. Together, these atlas studies provide a strong baseline for comparing healthy and disease-associated immune states.

Tumor Immune Microenvironment

Single-cell and spatial omics have substantially advanced understanding of the tumor immune microenvironment. The reviewed studies indicate that cancer progression and response to immunotherapy are shaped by heterogeneous immune populations, including exhausted T cells, macrophages, dendritic cells, natural killer cells, B cells, and other tumor-infiltrating immune subsets. Single-cell RNA sequencing has revealed that immune cells within tumors do not represent uniform populations but exist in diverse functional states that may promote or suppress antitumor immunity.

The integration of single-cell RNA sequencing with T cell receptor sequencing has provided deeper insight into clonotype dynamics and immune responses to checkpoint inhibitors. In non-small cell lung cancer, this approach revealed immune heterogeneity associated with variable responses to anti-PD-1 therapy. Spatial transcriptomics further demonstrated that tumor immunity is strongly influenced by tissue organization and cellular communication. Immunosuppressive populations such as SPP1-positive macrophages and FAP-positive cancer-associated fibroblasts were repeatedly identified across tumor contexts, suggesting their potential as therapeutic targets. These findings indicate that tumor immunity should be understood as a spatially organized ecosystem rather than a simple collection of immune cells.

Autoimmune Diseases

Single-cell multi-omics has also contributed significantly to the understanding of autoimmune disease mechanisms. Autoimmune diseases are characterized by complex interactions among genetic risk, environmental triggers, immune dysregulation, and tissue-specific inflammation. Conventional bulk approaches often fail to identify the specific immune subsets and tissue microenvironments responsible for disease activity. In contrast, single-cell technologies allow the identification of pathogenic immune states, inflammatory cell populations, and regulatory networks at high resolution.

In rheumatoid arthritis, single-cell transcriptomic analysis of synovial tissue has revealed fibroblast and macrophage subpopulations with distinct inflammatory or protective roles. In systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and related conditions, multi-omics approaches have supported biomarker discovery by integrating transcriptomic, proteomic, metabolomic, and epigenomic information. Spatial transcriptomics has further revealed localized immune structures and immunometabolic patterns within diseased tissues. In multiple sclerosis, single-cell spatial transcriptomics identified pathogenic inflammatory niches in chronic active lesions, including CD8-positive T cell niches associated with interferon signaling. These findings suggest that single-cell multi-omics may improve disease stratification, therapeutic monitoring, and cell-type-specific treatment development in autoimmune disorders.

Neuroimmunology

The reviewed studies show that neuroimmunology is an expanding field for single-cell and spatial omics applications. The central nervous system is no longer viewed as fully immune-privileged, but rather as a dynamic environment that interacts with peripheral immunity through microglia, astrocytes, the blood-brain barrier, and circulating immune cells. Single-cell and spatial transcriptomic technologies provide tools to examine these interactions in neurological and neurodegenerative diseases.

In neurological disease research, single-cell approaches help identify disease-associated glial and immune cell states, molecular drivers of inflammation, and patterns of immune infiltration. Integrated single-cell multi-omics in Alzheimer’s disease revealed a CD8-positive progenitor-exhausted T cell and monocyte interaction axis that may coordinate immune infiltration into the central nervous system. These findings suggest that peripheral immune dysfunction may contribute to neurodegenerative disease progression. Spatial omics is particularly relevant in neuroimmunology because the function of immune and glial cells is strongly influenced by their anatomical location. Therefore, single-cell and spatial technologies offer important opportunities for identifying biomarkers and therapeutic targets in neuroinflammatory and neurodegenerative diseases.

Emerging Trends and Future Perspectives

Across the reviewed literature, several emerging trends were identified. First, perturbational single-cell genomics, including CRISPR-based pooled screens and Perturb-seq, is becoming increasingly important for identifying causal gene functions in immune cells. Second, spatial multi-omics is moving toward higher resolution and greater molecular depth, enabling simultaneous mapping of transcriptomic and protein-level information within tissue architecture. Third, longitudinal single-cell studies are increasingly used to monitor immune dynamics before, during, and after therapeutic intervention.

Artificial intelligence and causal modeling are also emerging as central components of next-generation single-cell immunology. These approaches can help move the field beyond descriptive analysis by predicting cell behavior, identifying regulatory networks, and supporting drug discovery. However, clinical implementation remains challenging. High cost, batch effects, limited standardization, computational complexity, and the need for clinically validated biomarkers continue to limit the routine use of single-cell multi-omics in clinical medicine. Future progress will depend on the development of cost-effective platforms, standardized bioinformatics pipelines, reproducible analytical workflows, and stronger integration between omics data and clinical decision-making.

Overall Synthesis

Overall, the results of this review demonstrate that single-cell immunology and multi-omics provide a powerful framework for decoding immune complexity at unprecedented resolution. Across methodological, atlas-based, oncological, autoimmune, and neuroimmunological applications, these technologies consistently reveal cellular heterogeneity, disease-specific immune states, spatial immune niches, and molecular interaction networks that cannot be fully captured by conventional bulk methods. The evidence suggests that single-cell multi-omics is moving immunology toward a more precise, mechanistic, and clinically relevant understanding of immune function. Nevertheless, broader clinical translation requires continued efforts in standardization, validation, affordability, and interdisciplinary collaboration.

DISCUSSION

The present review demonstrates that single-cell immunology and multi-omics have transformed the understanding of immune system complexity by enabling molecular characterization at the resolution of individual cells. Across the reviewed literature, single-cell RNA sequencing, CITE-seq, spatial transcriptomics, and computational integration consistently reveal immune heterogeneity that cannot be captured using conventional bulk approaches. This finding is consistent with (Baysoy et al., 2023), who emphasized that single-cell multi-omics has expanded immunological analysis from transcriptomic profiling into integrated molecular characterization. Similarly, Song showed that CITE-seq improves immune cell identification by combining gene expression and surface protein information (Song et al., 2025). These developments indicate that modern immunology is moving from population-level analysis toward cell-resolved and systems-level immune profiling.

One important interpretation from this review is that technological advancement alone is not sufficient to explain immune complexity. The increasing volume and dimensionality of single-cell data require computational methods capable of integrating transcriptomic, proteomic, epigenomic, and spatial information. Schäfer argued that integrating single-cell multi-omics with prior biological knowledge can improve functional interpretation of immune responses (Schäfer et al., 2024). This view is supported by Yiu who highlighted the role of foundation models and artificial intelligence in cell annotation, trajectory inference, perturbation prediction, and multimodal integration (Yiu et al., 2025). Therefore, the progress of single-cell immunology depends not only on sequencing platforms but also on robust computational ecosystems that can translate complex datasets into biologically meaningful findings.

The findings of this review also show that immune atlas initiatives provide an important foundation for precision immunology. Atlas-based studies allow researchers to distinguish normal immune variation from disease-associated immune states. Xuan demonstrated that CITE-seq-based profiling of human hematopoietic progenitors can identify diverse progenitor and transitional immune cell populations (Xuan et al., 2024). Haniffa further showed that single-cell multi-omics can decode prenatal immune development and provide insight into early immune programming (Haniffa et al., 2025). In adult populations, Gong reported age-related immune dynamics through longitudinal multi-omic profiling (Gong et al., 2025). Compared with earlier immune profiling studies that mainly described broad cell populations, these atlas initiatives provide more detailed reference maps for understanding immune development, aging, and disease deviation.

In oncology, the reviewed evidence indicates that single-cell and spatial omics have substantially improved understanding of the tumor immune microenvironment. Ma reported that single-cell RNA sequencing reveals diverse immune cell functions and states within tumors, including tumor-infiltrating lymphocyte heterogeneity and T-cell exhaustion (Ma et al., 2025). Coffey similarly emphasized that spatial and single-cell approaches help explain immune organization within cancer tissues. Furthermore, Zheng showed that integrating single-cell and spatial transcriptomics can identify tumor-immune communication patterns and recurrent immunosuppressive cell populations (Zheng et al., 2025). These findings suggest that tumor immunity should not be understood only through immune cell abundance, but also through cell state, spatial position, and intercellular communication.

Single-cell multi-omics also provides important insights into autoimmune and neuroinflammatory diseases. In autoimmune disease, Zhu highlighted that single-cell technologies can reveal disease-specific immune subsets and pathogenic cellular states that are often hidden in bulk analyses (Zhu et al., 2025). Zhang further showed that multi-omics approaches support biomarker discovery in systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and related disorders. In neuroinflammation (Zhang et al., 2025), Feng identified pathogenic inflammatory niches in chronic active multiple sclerosis lesions using single-cell spatial transcriptomics (Feng et al., 2025). These findings indicate that tissue-specific immune dysregulation is shaped by both cellular identity and local microenvironmental context.

The review also confirms that neuroimmunology is becoming a major application area for single-cell and spatial omics. Wang explained that spatial transcriptomics and single-cell sequencing can identify molecular mechanisms involved in neuroimmune disorders (Wang et al., 2025). In Alzheimer’s disease, Zhao reported a CD8-positive progenitor-exhausted T cell and monocyte interaction axis that may coordinate immune infiltration (Zhao et al., 2026). This finding supports the idea that neurodegenerative diseases are not only driven by neuronal dysfunction but also by complex interactions between peripheral immune cells and the central nervous system. Compared with older concepts of the brain as an immune-privileged organ, recent single-cell evidence suggests a more dynamic model of brain-immune communication.

The novelty of this review lies in its integrated synthesis across technology, immune atlas construction, tumor immunology, autoimmune disease, and neuroimmunology. Previous reviews have often focused on specific technologies, such as single-cell multi-omics platforms or CITE-seq workflows (Baysoy et al., 2023; Song et al., 2025). Other reviews have emphasized computational methods or disease-specific applications (Ma et al., 2025; Schäfer et al., 2024). In contrast, the present review connects these domains into a broader translational framework. This approach highlights that the future of precision immunology will depend on the interaction between molecular technologies, computational interpretation, disease-specific validation, and clinical implementation.

Despite these advances, several limitations remain before single-cell multi-omics can be routinely applied in clinical practice. High cost, sample processing variability, batch effects, limited reproducibility, and lack of standardized analytical pipelines remain major barriers. These challenges are especially important because many single-cell biomarkers are still identified in discovery cohorts and require validation in larger and more diverse populations. In addition, current immune atlas projects remain unevenly distributed across global populations, which may reduce the generalizability of reference datasets. Therefore, future studies should prioritize multicenter validation, standardized workflows, inclusion of diverse populations, and integration with clinically interpretable outcomes.

The findings of this review have important implications for future biomedical research and healthcare policy. Single-cell multi-omics can support biomarker discovery, disease stratification, therapeutic target identification, and individualized treatment monitoring. However, successful clinical translation requires more than technological innovation. It requires investment in bioinformatics infrastructure, training of multidisciplinary experts, ethical governance of omics data, and development of cost-effective clinical assays. Future research should also strengthen longitudinal immune monitoring and perturbational single-cell studies to move from descriptive immune profiling toward causal and predictive immunology. Through these efforts, single-cell immunology can become a core component of next-generation precision medicine.

CONCLUSION

This review demonstrates that single-cell immunology and multi-omics have fundamentally reshaped contemporary immunological research by enabling comprehensive characterization of immune cells at single-cell resolution. The integration of transcriptomic, proteomic, epigenomic, and spatial information provides a more accurate understanding of immune heterogeneity, cellular interactions, and disease-specific molecular mechanisms than conventional bulk analytical approaches. Across the reviewed studies, these technologies consistently revealed important advances in human immune atlas construction, tumor immune microenvironment characterization, autoimmune disease pathogenesis, and neuroimmunology. Collectively, the evidence indicates that single-cell multi-omics has become an essential platform for advancing biomarker discovery, improving disease stratification, and supporting the development of precision immunology.

The principal scientific contribution of this review lies in its integrated synthesis of recent developments across multiple domains of single-cell immunology rather than focusing on a single technology or disease category. By combining evidence on technological innovation, computational integration, immune atlas initiatives, oncology, autoimmune diseases, and neuroimmunology, this review provides a broader conceptual framework that links methodological advances with translational and clinical applications. Furthermore, the review highlights the emerging role of artificial intelligence, systems immunology, and spatial multi-omics as complementary components of next-generation immunological research. This integrated perspective contributes to a more comprehensive understanding of how single-cell technologies are transforming both basic immunology and clinical decision-making.

This review has several limitations. The literature synthesis was restricted primarily to publications from 2024–2025, with a limited number of earlier landmark studies included to provide methodological context. In addition, as a narrative review, the findings depend on qualitative synthesis rather than quantitative meta-analysis and therefore may not capture all available evidence. Future reviews should incorporate broader literature coverage, formal quality assessment, and quantitative evidence synthesis where appropriate. Further research is also needed to evaluate the clinical implementation of single-cell multi-omics, particularly regarding biomarker validation, standardized analytical pipelines, cost-effectiveness, and integration into routine precision medicine across diverse healthcare settings.

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