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Review Article

Single-Cell and Spatial Omics in Hematopathology: From Cellular Heterogeneity to Precision Diagnostics

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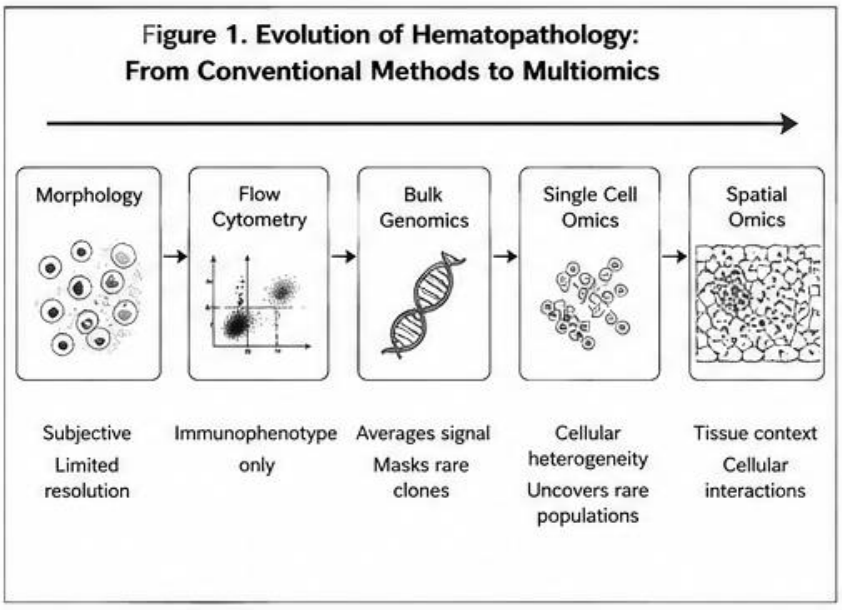
ABSTRACT:

Hematopathology has entered a new era with the emergence of single cell and spatial omics technologies, which provide unprecedented resolution for investigating cellular heterogeneity, clonal evolution, and tissue organization. Conventional diagnostic approaches, including morphology, immunophenotyping, flow cytometry, and bulk molecular analysis, have substantially advanced the diagnosis of hematologic disorders but often fail to capture rare cell populations and complex microenvironmental interactions. Single cell transcriptomics, chromatin accessibility profiling, and multimodal omics enable comprehensive characterization of individual cells, while spatial omics preserves tissue architecture and reveals the spatial distribution of malignant and nonmalignant cell populations. Together, these technologies have expanded the understanding of disease biology in acute myeloid leukemia, myelodysplastic syndromes, lymphomas, and other hematologic malignancies by identifying novel cellular states, early progenitor abnormalities, mechanisms of treatment resistance, and biomarkers associated with disease progression and therapeutic response. Integration of single cell and spatial datasets has also provided detailed insights into bone marrow niche organization and tumor microenvironment dynamics. Although challenges related to cost, standardization, computational analysis, and clinical implementation remain, ongoing technological advances are expected to facilitate broader diagnostic applications. This review summarizes the principles of single cell and spatial omics, highlights major discoveries in hematologic malignancies, and discusses their potential to refine disease classification, improve prognostic assessment, and support precision diagnostics in hematopathology.

Keywords: *Single cell omics; Spatial omics; Hematopathology; Acute myeloid leukemia; Myelodysplastic syndromes; Lymphoma; Precision diagnostics; Bone marrow microenvironmen*

1. INTRODUCTION:



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Hematopathology relies on the ability to interpret diverse cell populations. Conventional techniques, such as morphology, immunohistochemistry, flow cytometry, and bulk genomics, have provided major insights; however, each has limitations. Bulk sequencing masks the minority clones. Morphology can be subjective. Flow cytometry resolves immunophenotypes but not transcriptional programs. These gaps are particularly relevant in diseases such as acute myeloid leukemia [AML], myelodysplastic syndromes [MDS], and lymphomas, where heterogeneity drives relapse, resistance, and transformation [1].

The rise of single-cell technologies has provided a unique opportunity to dissect hematologic diseases at an unprecedented depth [2]. Single-cell RNA sequencing [scRNA-seq], single-cell chromatin analysis, and multiomic profiling allow investigators to measure the genetic, transcriptional, and epigenetic states of thousands to millions of individual cells. Spatial transcriptomics and imaging mass cytometry then map these cellular states back into tissue context, revealing patterns of interaction that were previously hidden [3].

Hematopoietic tissues naturally lend themselves to single-cell profiling because they contain fluid, dissociable cell populations with rich lineage diversity. Within the last five years, single-cell studies have redefined several core concepts in hematopathology. Investigators have identified early abnormal progenitor states in MDS, discovered drug-resistant stem like subclones in AML, mapped tumor microenvironments in lymphomas, and built detailed atlases of human bone marrow architecture [4].

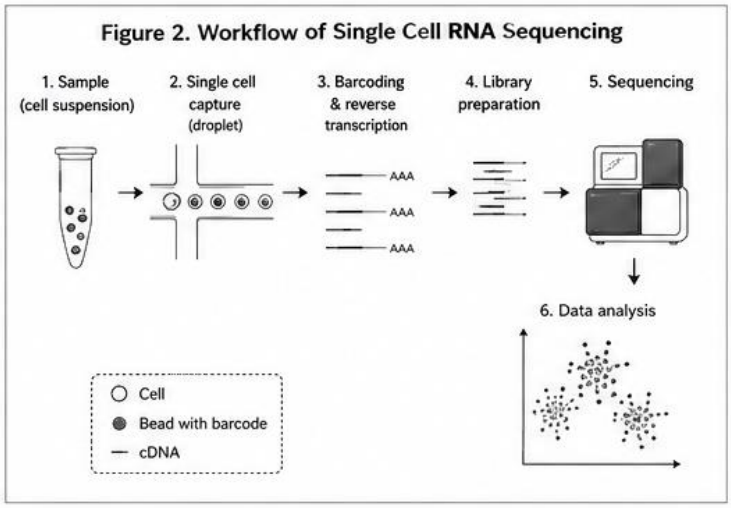
This Chapter aims to provide an integrated narrative of how single-cell and spatial omics are reshaping hematopathology by introducing new diagnostic dimensions, revealing disease trajectories, and offering clinically relevant biomarkers.

2. Principles of Single Cell Omics

Single cell RNA sequencing

Single-cell RNA sequencing has become the most widely used single-cell technique. This method involves capturing individual cells, reverse-transcribing RNA, barcoding molecules, and sequencing the resulting libraries. High throughput droplet methods such as 10x Genomics Chromium are now standard because they process large numbers of cells at reasonable cost [5].

scRNA-seq resolves transcriptional programs that define lineage identity and activation states. In hematology, this has allowed mapping of progenitor hierarchies, characterization of rare leukemic stem cell compartments, and identification of inflammatory states that contribute to disease progression [6].



Single cell ATAC sequencing

Single-cell ATAC-seq measures chromatin accessibility at single-cell resolution. It identifies regulatory regions, open chromatin sites, and transcription factor motifs. These datasets complement scRNA seq by revealing upstream

regulatory landscapes [7]. Many studies in MDS and AML show that chromatin changes precede transcriptional abnormalities, suggesting that regulatory shifts may represent early disease states [8].

Multiomic single cell approaches

Several platforms combine more than one modality. CITE-seq links surface protein markers to transcriptomic profiles using DNA-barcoded antibodies. This bridges flow cytometry with single cell transcriptomics and is valuable when immunophenotyping is essential for classification [9]. Other methods combine ATAC data with RNA, methylation, or TCR/BCR sequencing data. Multiomic assays can distinguish clonal subpopulations and map lineage relationships in complex samples such as bone marrow [10].

Figure 3. Comparison of scRNA-seq, scATAC-seq and Multiomic Approaches

	scRNA-seq	scATAC-seq	Multiomic (RNA + ATAC)
What it measures	Gene expression	Chromatin accessibility	Gene expression + Chromatin accessibility
Input	RNA	Accessible chromatin	RNA + Open chromatin
Output			
Biological insight	Active genes Cell states	Regulatory elements TF binding sites	Integrated view of regulation and expression
Resolution (single cell)	High	High	High

Computational analysis

Single-cell data require substantial computational processing. The typical steps include quality filtering, normalization, clustering, dimensionality reduction, and annotation. Pseudotime analysis reconstructs developmental trajectories, while RNA velocity predicts lineage direction [11]. Batch correction and integration frameworks have improved cross-sample comparisons. Despite this progress, computational complexity remains a barrier for diagnostic laboratories [12].

3. Principles of Spatial Omics

Unlike single-cell assays that dissociate tissues, spatial omics preserves spatial relationships. This is critical in hematopathology because malignant and nonmalignant cells interact within structured microenvironments [13].

Spatial transcriptomics

Spatial transcriptomics methods, such as the 10x Visium platform, place barcoded oligonucleotide arrays beneath tissue sections. The transcripts retain spatial information. Although resolution is limited by spot size, the method captures gene expression landscapes across tissue architecture[3]. High resolution techniques such as Slide seq and HDST extend this concept with finer bead grids[14] .

Imaging mass cytometry

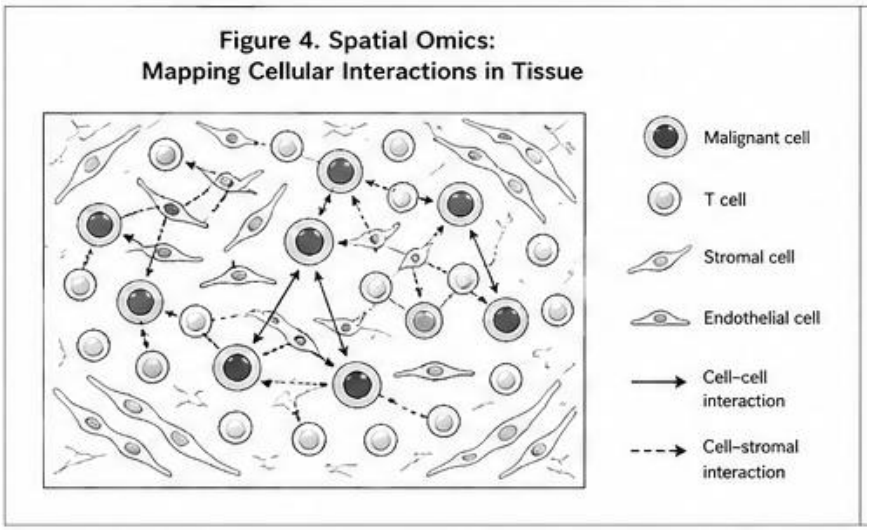
Imaging mass cytometry uses metal isotope-labeled antibodies and laser ablation to quantify more than 40 markers at subcellular resolution. It is particularly useful in lymphomas because it simultaneously resolves tumor cells, immune cells, stromal populations, and their interactions [15].

Multiplex immunofluorescence

Technologies such as CODEX and MIBI provide iterative staining cycles that generate high-plex protein maps. These techniques retain morphological detail and permit cell neighborhood analysis [16].

Integration with single cell data

Spatial omics is often integrated with scRNA-seq spatial maps to guide the annotation of transcriptional clusters and identify which cell states occupy specific niches. This combined approach is essential for interpreting bone marrow biopsies where diverse lineages coexist [12].



A comparative summary of major single-cell and spatial omics technologies, including their outputs, clinical applications, and limitations, is presented in Table 1.

Table 1. Comparison of Single Cell and Spatial Omics Technologies

Technology	Key Output	Clinical Utility	Limitation
scRNA-seq	Gene expression	Identify subclones	No spatial context
scATAC-seq	Chromatin state	Early disease detection	Complex analysis
Spatial omics	Tissue architecture	Microenvironment analysis	Lower resolution
Multiomics	Integrated data	Precision diagnosis	Expensive

These technologies have enabled deeper insights into disease biology, particularly in myeloid malignancies, such as acute myeloid leukemia.

4. Single Cell Discoveries in Myeloid Neoplasms

The application of single cell and spatial omics technologies has provided critical insights into the biological complexity of hematologic malignancies Among these, myeloid neoplasms such as acute myeloid leukemia and myelodysplastic syndromes have been extensively studied due to their marked cellular heterogeneity and clinical variability [17] [18].

Heterogeneity in AML

AML is a heterogeneous disease at the genetic and transcriptional levels. Early single-cell studies revealed that leukemic blasts contain multiple differentiation states that may coexist in individual patients. Van Galen and colleagues used scRNA seq to profile primary AML and reported at least six malignant transcriptional programs including stem like, progenitor like, and differentiated states that varied across patients. This work also showed that stem like transcriptional signatures were associated with inferior prognosis [19].

Subsequent studies have identified rare leukemic stem cell populations with unique regulatory features. These stem-like cells often persist after therapy and are likely to contribute to relapse. scRNA-seq has also been used to characterize the response to targeted therapy. For example, Duncan et al. studied FLT3 mutated AML treated with FLT3 inhibition and found that resistant subclones shifted into stem like or monocytic states depending on microenvironmental cues [20].

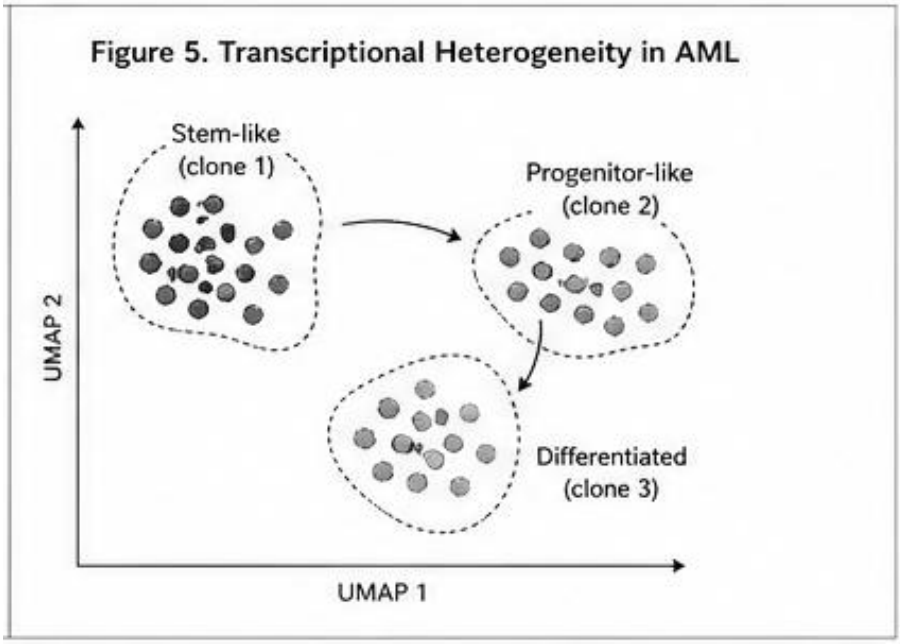
MRD detection and relapse prediction

Single-cell approaches have revealed minimal residual disease at levels undetectable by flow cytometry. Granja et al. integrated scATAC-seq and scRNA-seq to show that chromatin states in

AML correlate with relapse risk and may precede transcriptional relapse signatures. These findings suggest that pre relapse regulatory programs might be used as biomarkers for early intervention [21].

AML microenvironment

Spatial omics have shown that bone marrow niches influence acute myeloid leukemia [AML] progression. Kfoury et al. demonstrated that AML remodels stromal niches, reduces osteoblast populations, and alters cytokine gradients. Spatial transcriptomics confirm that leukemic blasts cluster near vascular niches rich in CXCL12 and other supportive factors [22].



5. Single Cell Insights in Myelodysplastic Syndromes

Early abnormal progenitor states

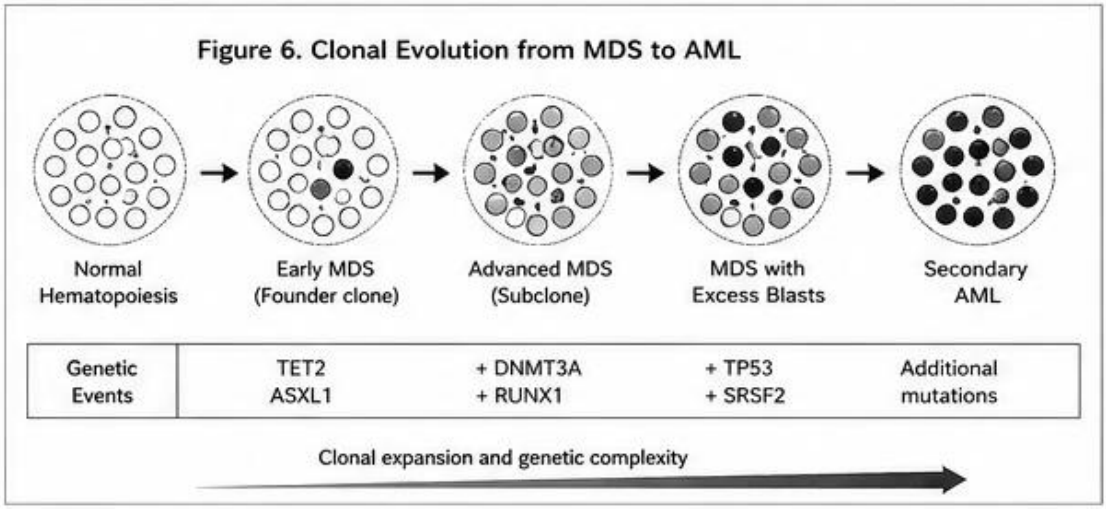
One of the most significant contributions of single-cell analysis to hematology is the discovery of abnormal progenitor populations in MDS. Pellin et al. mapped bone marrow progenitors in MDS and identified aberrant progenitor states that diverged from normal hematopoiesis. These states were enriched for inflammatory gene programs, suggesting that inflammation plays a key role in early disease stages [23].

Chromatin remodeling and lineage skewing

scATAC-seq studies have shown that MDS progenitors possess distinct chromatin accessibility patterns that bias differentiation toward myeloid fates. These regulatory changes are partly driven by mutations in epigenetic regulators, such as TET2, ASXL1, and SRSF2. Importantly, epigenetic alterations often appear in hematopoietic stem cells long before clinical disease is evident [24].

Predicting transformation to AML

Single-cell multiomic studies can predict the risk of transformation. Chen et al. demonstrated that emergent stem like clones with specific transcription factor programs preceded progression from MDS to AML. This may be clinically important for identifying high risk patients who require early therapeutic intervention[25].



While myeloid neoplasms have provided key insights into clonal evolution, similar approaches have advanced our understanding of lymphoid malignancies.

6. Applications in Lymphoid Neoplasms

Tumor microenvironment in lymphomas

Single-cell studies have transformed our understanding of the lymphoma microenvironment. In follicular lymphoma [FL], scRNA-seq has identified distinct T follicular helper cell subsets, exhausted cytotoxic cells, and suppressive macrophages that shape tumor behavior. Kotlov et al. analyzed FL across multiple cohorts and identified four microenvironmental archetypes with prognostic significance [26].

In diffuse large B-cell lymphoma [DLBCL], single-cell analysis reveals strong variations in immune infiltration. Some tumors exhibit immune-rich microenvironments, whereas others are immune-cold. These patterns correlate with response to immunotherapy [27].

Spatial mapping of lymphoma architecture

Imaging mass cytometry has been particularly useful in lymphomas because these diseases exhibit a structured tissue architecture. Highly multiplexed protein maps reveal the arrangement of malignant B cells around stromal networks and immune zones. Schurch et al. used multiplexed imaging to map the cellular ecosystem of Hodgkin lymphoma and revealed that Reed Sternberg cells form clusters surrounded by specific T cell subsets [28].

Clonal diversity in T cell neoplasms

T-cell lymphomas often exhibit complex clonal structures. Single-cell TCR sequencing uncovers multiple malignant clones and distinct differentiation states. These analyses highlight the need for revised diagnostic classification that accounts for transcriptional and clonal heterogeneity [29]

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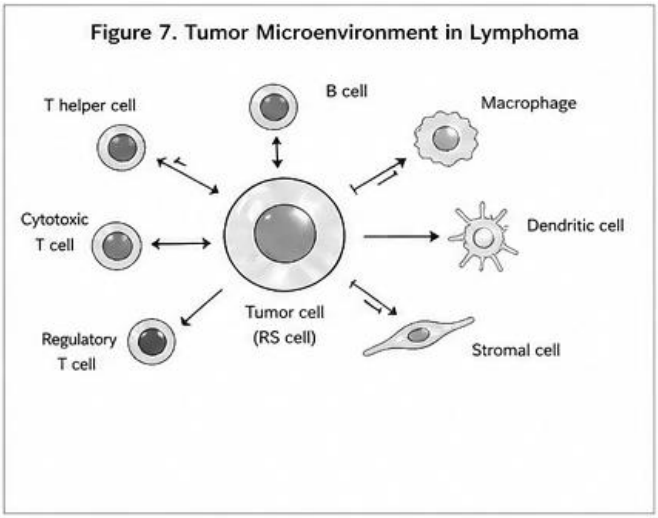


7. **Mapping the Bone Marrow Microenvironment**

Beyond intrinsic tumor heterogeneity, the bone marrow microenvironment plays a central role in regulating hematopoiesis and shaping malignancy evolution. Single-cell and spatial studies have refined our understanding of the marrow niches[30].

Normal hematopoietic architecture

Baccin et al. generated a spatial and single cell atlas of human bone marrow, identifying stromal, endothelial, and immune cell subsets with region specific organization. HSCs localize near sinusoidal endothelium, while committed progenitors show distinct spatial gradients [4].

Remodeling during leukemia

AML and MDS disrupt the microenvironmental circuits. Neoplastic cells alter cytokine production, remodel the extracellular matrix, and suppress normal hematopoiesis. Spatial transcriptomics demonstrates that leukemic clusters create micro niches with high metabolic activity and inflammatory cytokines [31].

Immune dysregulation

Single-cell studies have shown increased inflammatory monocytes, exhausted NK cells, and dysfunctional T cells in MDS and AML. These changes may contribute to ineffective hematopoiesis and impaired immune surveillance [32].

8. Diagnostic Transformation

Single-cell and spatial technologies have many potential diagnostic applications, although most are not yet routine.

Refined disease classification

Newly identified transcriptional states may eventually define the diagnostic subclasses. For example, stem-like AML programs may represent a biologically distinct group with specific therapeutic vulnerabilities. In MDS, aberrant progenitor signatures can identify early disease even when morphology is subtle [33].

Digital immunophenotyping

CITE-seq and multiplex imaging bridge immunophenotyping with transcriptomic data. These methods can be used to refine ambiguous flow cytometry findings. In the long term, digital immunophenotyping may complement or replace some flow cytometry assays[34].

Tissue based spatial diagnostics

Spatial transcriptomics and imaging mass cytometry can detect patterns that are difficult to observe using routine histology. For example, the spatial proximity of tumor cells to suppressive macrophages may predict the response to immunotherapy. The diagnostic implications of these technologies naturally extend to clinical applications, including biomarker development and therapeutic monitoring[35] .

9. Clinical Translation

Biomarker discovery

Single-cell-derived markers may improve diagnosis and therapy selection. Predictive gene signatures for AML relapse have emerged. Spatial biomarkers such as immune neighborhood patterns, may inform lymphoma prognosis [36].

Treatment response

scRNA-seq can track the real-time response of leukemia to therapy. These approaches reveal resistant subclones early, allowing for potential treatment adjustment.

CAR T cell therapy

Single-cell profiling of CAR T infusion products predicts response and toxicity. Pre-infusion signatures correlate with long-term remission in B cell malignancies. Spatial studies also show how CAR T cells infiltrate tumors and interact with resident immune cells[37].

Key disease-specific discoveries and their translational relevance derived from single-cell technologies across hematologic malignancies are summarized in Table 2.

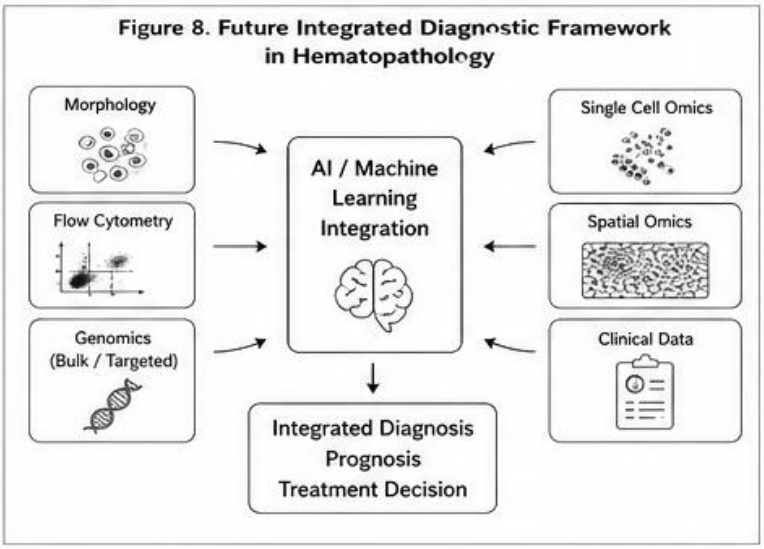
Table 2. Key Discoveries Using Single Cell Technologies in Hematologic Malignancies

Disease	Discovery	Clinical Impact
AML	Stem-like clones	Predict relapse
MDS	Aberrant progenitors	Early detection
Lymphoma	Immune niches	Prognosis
CAR-T therapy	Cellular signatures	Therapy response

10. Integration with Artificial Intelligence

Artificial intelligence and machine learning are essential for large-scale omics integration. Deep learning tools help classify cell states, infer lineage relationships, and combine multi-omic data with digital pathology. Several groups have created computational frameworks that integrate morphology with scRNA seq and spatial maps, generating holistic diagnostic predictions [38].

Although promising, these AI tools need validation across diverse populations and real-world samples [39].



11. Limitations and Challenges

Several obstacles prevent the widespread clinical use of single-cell and spatial omics.

- The cost of sequencing and imaging platforms remains high.
- Sample processing affects the cell viability and transcriptome profiles.
- Batch effects introduce variability that complicates comparisons across centers.
- Data scaling requires a specialized computational infrastructure.
- Lack of regulatory pipelines for diagnostic purposes.
- Interpretation complexity requires training, which most laboratories do not yet possess.

Despite these challenges, continuous improvements in chemistry, automation, and informatics have accelerated progress in this field.

12. Future Directions

Several emerging directions may further transform hematopathology in the future.

- 3D spatial transcriptomics will map the entire marrow niches in volumetric detail.
- Real-time single-cell sequencing may enable point-of-care MRD monitoring.
- Liquid biopsy single-cell analysis can detect circulating leukemic progenitors.
- Integrated clinical platforms may combine morphological, flow cytometry, genomic, and spatial data into unified diagnostic reports.
- Hematopoietic cell atlases serve as reference standards for disease classification.

Over time, hematopathology may shift from descriptive categories to dynamic, state-based taxonomies informed by single-cell biology.

13. Conclusion

Single cell and spatial omics have opened a new era for hematopathology. These technologies reveal cellular states, clonal structures, and tissue architectures that are invisible to conventional tools. These studies provide insights into how malignant clones evolve and how the microenvironment shapes disease behavior. Although clinical translation is still limited, the trajectory is clear. In the coming decade, hematopathology will increasingly integrate multiomics data into diagnosis and treatment planning. This transformation promises greater precision and a deeper understanding of hematologic disease. The integration of these technologies into routine hematopathology practice will enable a transition toward precision, biology-driven, diagnostic frameworks.

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