(S124) TRANSCRIPTIONALLY DEFINED AML CELL STATES ASSOCIATE WITH TREATMENT RESPONSE AND MICROENVIRONMENTAL REMODELING

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

Acute myeloid leukemia (AML) is a molecularly and phenotypically heterogeneous malignancy with poor prognosis. Although therapy resistance is often attributed to leukemic stem cells (LSCs), AML cell identity and function extend beyond classical surface marker definitions. Emerging evidence suggests that leukemic cell states interact dynamically with the bone marrow microenvironment, influencing cytokine signaling, niche remodeling, and drug response. However, a functional classification of AML cell states and their clinical relevance remains incompletely defined.

Aims

We aimed to define transcriptionally and functionally distinct AML cell states and explore how they modulate the microenvironment, influence therapy response, and associate with clinical outcome.

Methods

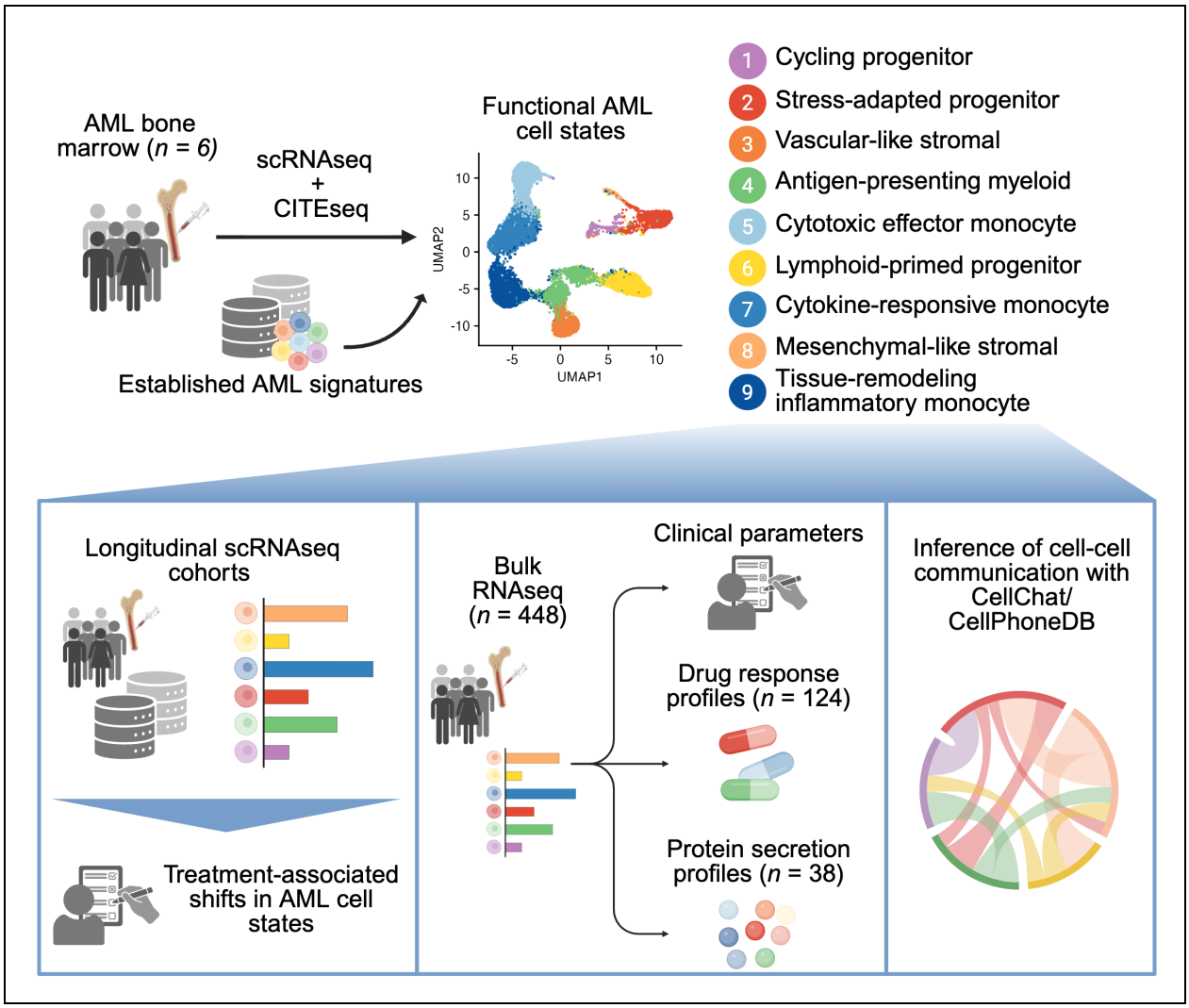
Integrated scRNA-seq and CITE-seq were performed on diagnostic AML samples (n=6). Myeloid clusters were annotated using AML reference atlases and evaluated for stemness using established HSC/LSC signatures. State-specific gene signatures were projected onto bulk RNA-seq cohorts (n=448) to assess associations with ex vivo drug sensitivity (n=124), soluble proteomics (n=38), and clinical parameters. Public longitudinal single-cell datasets were used to validate findings and analyze therapy-induced shifts in cell-state composition. Cell-cell communication was inferred using CellChat and CellPhoneDB.

Results

Clustering resolved nine conserved AML cell states across patients, including progenitor-like (cycling, stress-adapted, lymphoid-primed), stromal-like (vascular, mesenchymal), and multiple specialized monocytic or differentiated programs (antigen-presenting, cytotoxic effector, cytokine-responsive, tissue-remodeling inflammatory). CITE-seq confirmed transcript-protein concordance while revealing heterogeneity within CD34/CD38-defined populations. Stemness signatures were distributed across several cell states, indicating that LSC features are not confined to a single immunophenotypic compartment. Cell states were also defined by distinct transcriptional programs, enabling derivation of compact 20-gene signatures. Projection of state-specific signatures onto bulk RNA-seq revealed heterogeneous patient-level enrichment and distinct associations with drug sensitivity, revealing state-specific sensitivity and resistance patterns (e.g. crenolanib sensitivity in cycling progenitors). In longitudinal datasets, induction chemotherapy mainly reduced lymphoid-primed progenitors and cytotoxic effector monocytes, whereas cycling progenitor and antigen-presenting myeloid states persisted post-treatment. Venetoclax/azacitidine treatment differentially affected progenitor, stromal, and monocytic states, showing most persistence of the stress-adapted progenitors. Communication analysis predicted state-specific immune and niche signaling differences (e.g. NOTCH, THBS, ANGPT).

Summary/Conclusion

We define nine functional AML cell states that integrate lineage identity, stemness programs, and microenvironmental signaling properties. Stem-like features are embedded across multiple transcriptional states and are not adequately captured by classical surface/transcription markers alone. These states associate with drug sensitivity patterns, display treatment-specific persistence dynamics, and exhibit distinct niche-interacting programs. Functional state stratification therefore extends beyond the traditional leukemic stem cell paradigm and provides a biologically grounded framework for refining therapeutic targeting in AML.



Study design and overview