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Review Article

Single-Cell Transcriptomic Profiling of Leukemic Stem Cell Populations in Acute Myeloid Leukemia

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Summary

Leukaemic stem cells have been defined by an immunophenotype for nearly three decades. Single-cell sequencing shows that definition failing in both directions at once: it contains normal stem cells that should not be there, and misses leukaemic ones that lie outside the gate.

Objectives: To review the published evidence from single-cell transcriptomic profiling of leukaemic stem cell populations in acute myeloid leukaemia: what cellular states have been resolved, how they relate to the immunophenotypic definition, what they reveal about chemoresistance, and whether the findings support a universal marker or a patient-specific one.

Material and Methods: Narrative review of single-cell sequencing studies, functional xenograft work, stemness score derivations and cellular hierarchy analyses indexed in PubMed and the major haematology and genomics journals. Studies were eligible if they characterised leukaemic stem or progenitor populations in acute myeloid leukaemia by single-cell methods, or established the phenotypic and functional definitions those methods have tested. No new patient data were generated and no patients were recruited; every finding quoted is one published by the original investigators.

Results: Integrating single-cell mutation detection with transcriptomes across sixteen patients resolved six malignant cell types resembling normal counterparts along the differentiation axis, from stem-cell-like through progenitor, granulocyte-monocyte progenitor, promonocyte and monocyte to dendritic-cell-like, with strikingly heterogeneous abundance between tumours: some comprised one or two types, others a full range. Leukaemic stem cells constitute under 10 per cent of malignant CD34-positive blasts. A quiescent immature stem-cell-like population was identified carrying raised AP-1 transcription factor expression and reduced class II major histocompatibility expression. A previously described surface marker was upregulated in only one of four patients examined. In thirteen paired pre- and post-chemotherapy paediatric samples, approximately half of leukaemic stem and progenitor populations actively expressed stem cell and oxidative phosphorylation signatures and showed enhanced metabolic programmes under treatment.

Conclusion: The historical CD34-positive CD38-negative definition encompasses normal haematopoietic stem cells while missing leukaemic cells outside that compartment. Marker expression appears patient-specific rather than universal, which constrains what any single-marker targeting strategy can achieve.

Abbreviations: AML – Acute Myeloid Leukaemia, LSC – Leukaemic Stem Cell, HSC – Haematopoietic Stem Cell, LSPC – Leukaemic Stem and Progenitor Cell, scRNA-seq – Single-Cell RNA Sequencing, GMP – Granulocyte-Monocyte Progenitor, cDC – Conventional Dendritic Cell, OXPHOS – Oxidative Phosphorylation, MHC – Major Histocompatibility Complex, AP-1 – Activator Protein 1, MRD – Measurable Residual Disease, NOD/SCID – Non-Obese Diabetic Severe Combined Immunodeficiency.

Keywords: Acute Myeloid Leukaemia; Leukaemic Stem Cells; Single-Cell RNA Sequencing; Cellular Hierarchy; Chemoresistance

Introduction

Acute myeloid leukaemia is a heterogeneous disease of haematopoietic stem cells in which functionally distinct populations coexist within a single patient's marrow [1,2]. A substantial proportion of patients resist induction chemotherapy, and outcome on relapse remains poor, which has directed attention toward the subpopulation responsible for regenerating the disease [3,4].

That subpopulation was identified functionally. Transplantation experiments in immunodeficient mice showed that a CD34-positive CD38-negative blast population could reconstitute human acute leukaemia, and those cells were accordingly termed leukaemic stem cells by analogy with the self-renewing normal cells that reconstitute haematopoiesis [5,6]. They are rare, comprising under 10 per cent of malignant CD34-positive blasts, and are hidden within the bulk tumour mass [7,8].

The phenotype has since served as both a research definition and a therapeutic target [9,10]. Single-cell RNA sequencing now permits high-resolution interrogation of cellular heterogeneity and transcriptional state within the leukaemic ecosystem [1,11], and applying it to this question has produced findings that the phenotypic definition does not accommodate.

This review sets out what cell states single-cell profiling has resolved, how they map onto the historical definition, what they show about chemoresistance, and whether the evidence supports a universal marker.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and genomics journals were searched for single-cell studies of leukaemic stem cells. Search terms combined acute myeloid leukaemia with single-cell RNA sequencing, leukaemic stem cell, cellular hierarchy, stemness score, transcriptomic heterogeneity and chemoresistance. Reference lists of retrieved atlases and functional studies were screened by hand.

Eligibility: Studies were included if they characterised leukaemic stem or progenitor populations in acute myeloid leukaemia using single-cell methods, derived or validated a stemness score, or established the phenotypic and functional definitions against which single-cell findings are read. Studies in murine models and xenografts are cited where they established the functional definition and are identified as such.

Data extraction and handling: Platform, number of patients, cell numbers, enrichment strategy, and reported cell states or signatures were extracted as published. The number of patients profiled is stated alongside every finding, because several influential observations rest on very small cohorts and their generalisability is the principal open question in this field. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published findings only. This is a narrative synthesis and was not registered as a systematic review.

Results

What single-cell profiling resolved: Integrating single-cell mutation detection with transcriptomes across sixteen patients classified six types of malignant cell resembling normal counterparts

along the differentiation axis from haematopoietic stem cell to myeloid lineage: stem-cell-like, progenitor-like, granulocyte-monocyte progenitor-like, promonocyte-like, monocyte-like and conventional dendritic cell-like (Figure 1) [12].

The finding that carries most weight is not the taxonomy but the variation within it. Relative abundances of these cell types were strikingly heterogeneous between tumours: some consisted of one or two dominant types, while others contained the full range [12]. Two patients sharing a diagnosis and a genotype may therefore have quite different cellular compositions.

Subsequent work established a cellular hierarchy framework for understanding that heterogeneity and predicting drug response [13], and multimodal atlases have defined primitive compartments and their marker sets, mapped how bulk stemness scores project onto particular primitive states, and identified therapy-resistant states not previously recognised [14].

SIX MALIGNANT CELL STATES RESOLVED IN ONE COHORT

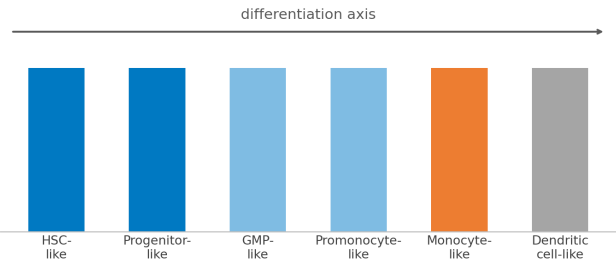


Figure 1: Malignant cell states resolved along the differentiation axis across sixteen patients [12]

The definition fails in both directions: The historical immunophenotypic definition has proved insufficient for precise identification and targeting, because the CD34-positive CD38-negative population encompasses both leukaemic stem cells and normal haematopoietic stem cells, while simultaneously missing leukaemic stem cells residing outside that phenotypic compartment (Figure 2) [14].

Those are two distinct failures with different consequences. Including normal stem cells means any therapy directed at the gate will damage normal haematopoiesis, which has constrained the development of stem-cell-directed treatment [9,14,15]. Excluding leukaemic cells outside the gate means the population being studied is not the population responsible for relapse.

Single-cell comparative analyses of leukaemic against normal stem cells have revealed numerous functionally validated surface markers permitting more specific discrimination [14,16], and subsets with distinct transcriptional, epigenetic and functional properties have been identified within what was previously treated as one population [16].

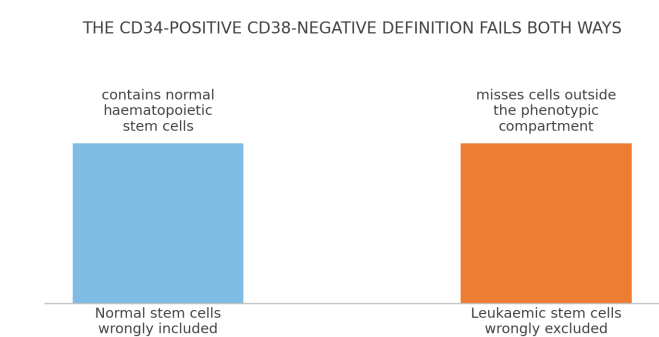


Figure 2: The two ways in which the phenotypic definition misclassifies [14]

Study	Patients	Method	Principal reported finding
Bonnet and Dick 1997 [5]	—	Xenograft	CD34+CD38- population reconstitutes leukaemia
Ng et al. 2016 [17]	Cohort	Expression	Seventeen-gene stemness score derived
van Galen et al. 2019 [12]	16	scRNA-seq	Six malignant cell states; abundance highly variable
Velten et al. 2021 [18]	4	scRNA-seq	Quiescent stem-like cells with raised AP-1 factors
Zeng et al. 2022 [13]	Cohort	Hierarchy model	Framework predicting drug response from composition
Paediatric cohort 2023 [19]	13	Paired scRNA-seq	Half of stem populations carry resistance signatures

Table 1: Principal studies reviewed, with method and the finding as reported by the original investigators

How rare the population is: Leukaemic stem cells comprise under 10 per cent of malignant CD34-positive blast cells and remain restricted to an immature phenotype resembling normal stem cells while retaining self-renewal and partial differentiation capacity (Figure 3) [7,8]. That rarity is the technical reason single-cell methods were needed: a population at this frequency is invisible to bulk transcriptomics, which averages it away [1,11].

Frequency measured by flow cytometry at diagnosis independently predicts outcome [20], and residual disease assessment has converged on stem-cell-like subpopulations as contributing the greatest discriminatory accuracy in surveillance [21,22]. The population is therefore clinically consequential as well as biologically distinct.

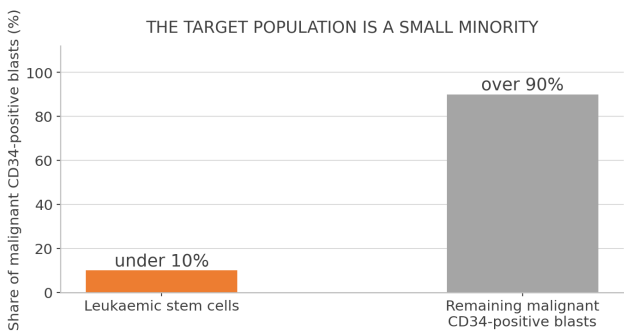


Figure 3: Leukaemic stem cells as a proportion of malignant CD34-positive blasts [7,8]

What the resistant state looks like: Integrated data from four patients alongside normal marrow CD34-positive cells revealed a subpopulation of quiescent immature stem-cell-like leukaemic cells characterised by increased expression of AP-1 transcription factors, including FOS, JUN, FOSB, JUNB and JUND, together with decreased class II major histocompatibility expression [18].

The reduction in class II expression is notable because it bears on immune recognition: a cell displaying less antigen is less visible to the T-cell compartment, which links the resistant transcriptional state to immune escape rather than to drug handling alone [12,18]. In normal karyotype disease, a presumed stem cell cluster was identified expressing CD34, CD38, CD96, CD46, CD47, CD82, CD44 and CD133 [23].

Paired sampling before and after chemotherapy in thirteen children who achieved remission found that approximately half of leukaemic stem and progenitor populations actively expressed stem cell and oxidative phosphorylation signatures respectively, and that these clusters had a higher chance of tolerating therapy while exhibiting an enhanced metabolic programme in response to treatment (Figure 4) [19].

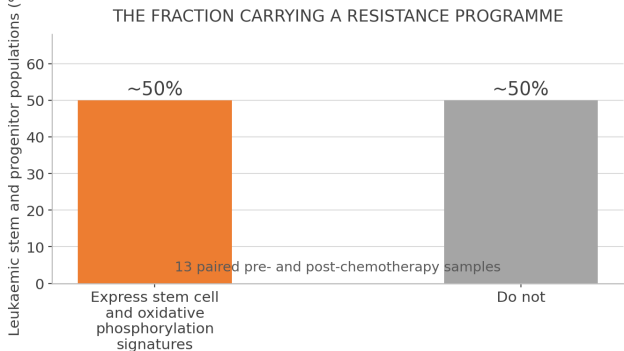


Figure 4: Leukaemic stem and progenitor populations carrying resistance signatures in paired paediatric samples [19]

Whether the markers are universal: This is where the single-cell data are most awkward for the field. A previously described stem

cell marker was upregulated in only one of the four patients examined, leading the investigators to suggest that leukaemic stem cells might themselves be patient-specific [18,23]. If so, a marker validated across a cohort may identify the relevant population in only a subset of individuals.

The observation rests on four patients and requires validation in larger cohorts before its general applicability can be determined, a caveat the original investigators state explicitly [18,23]. It is nonetheless consistent with the compositional heterogeneity reported across sixteen patients, where the dominant malignant cell type differed between tumours [12].

Approach	What it identifies	Limitation
CD34+CD38-phenotype	A compartment containing leukaemic stem cells	Includes normal stem cells; misses some leukaemic ones [5,14]
Xenograft repopulation	Functionally defined stem cells	Slow; murine niche; not clinically deployable [5,6]
Bulk stemness score	Aggregate stemness of a sample	Averages across cell states [14,17]
Single-cell transcriptomics	Individual cell states and their abundance	Small cohorts; patient-specific findings [12,18]

Table 2: Approaches to identifying leukaemic stem cells and what each can establish

Where relapse originates: Tracking clonal composition from diagnosis into relapse located the origin within the stem compartment rather than in the bulk population [27], and preleukaemic haematopoietic stem cells carrying founder mutations were shown to precede overt disease [28] and to persist through remission [29]. The population that survives treatment is therefore continuous with the population that started the disease.

Detecting expressed mutations directly in single cells has made it possible to assign malignancy without inferring it from transcriptional profile alone [23], which addresses one of the principal technical objections to earlier work. Genomic classification of the disease provides the framework against which these cellular findings are read [26].

Stemness scores derived from bulk expression bridge the research and clinical settings. A seventeen-gene score permits rapid risk assessment [17] and has been implemented as a laboratory-developed assay [24], while hierarchically organised patient-derived models allow the underlying biology to be interrogated experimentally [25].

Metabolism as the tractable target: If the resistant state is defined by oxidative metabolism rather than by a surface marker, then metabolism rather than phenotype is what should be targeted. Chemotherapy-resistant cells were shown not to be enriched for stem

cells as conventionally defined but to require oxidative metabolism [30], which reframes the target away from a cell type toward a cell state.

That reframing has already produced an intervention. BCL-2 inhibition targets oxidative phosphorylation and selectively eradicates quiescent stem cells [31], and the endosteal localisation of chemotherapy-resistant cells supplies a complementary anatomical target [32]. Both approaches sidestep the marker problem entirely.

Observation	Implication	Source
Relapse originates in stem compartment	Targeting bulk disease is insufficient	Clonal tracking [27]
Preleukaemic clones persist in remission	Remission does not clear the founding population	Sequencing in remission [28,29]
Resistant cells require oxidative metabolism	State rather than phenotype is the target	Functional studies [30]
BCL-2 inhibition eradicates quiescent cells	A metabolic route already exists	Preclinical and clinical [31]

Table 3: What the wider literature adds to the single-cell findings

Discussion

Single-cell profiling has done something unusual for a new technology: rather than refining an existing definition, it has shown that definition to be wrong in two directions simultaneously. The CD34-positive CD38-negative gate contains cells it should not and excludes cells it should not [14].

That matters because the phenotype has been the basis for both research sampling and therapeutic targeting for nearly three decades [5,9]. A study sorting on the gate has been enriching for a mixture, and an antibody directed at the gate would deplete normal haematopoiesis alongside the malignant population [14,15].

If stem cell states are patient-specific

The suggestion that leukaemic stem cells may be patient-specific [18] would, if confirmed, reframe the therapeutic problem. A universal stem-cell-directed agent presupposes a universal target, and the single-cell data do not currently support one: marker expression varied between patients and compositional structure varied between tumours [12,18,23].

The alternative it implies is per-patient characterisation, which is technically feasible but has no established clinical pathway. Cellular hierarchy frameworks that predict drug response from composition rather than from a single marker are the nearest available approach [13], and they treat heterogeneity as the signal rather than as noise to be averaged out.

Why the resistance findings converge

Two independent observations point the same way. The quiescent stem-like population carries raised AP-1 factors and reduced antigen presentation [18], and roughly half of leukaemic stem and progenitor populations carry oxidative phosphorylation signatures with enhanced metabolic response to treatment [19]. Quiescence, altered metabolism and reduced immune visibility describe a coherent phenotype.

This aligns with what is known from other directions: stem cell frequency at diagnosis predicts outcome [20], and stem-cell-like subpopulations contribute most to residual disease discrimination [21,22]. The cell identified transcriptionally as resistant is the cell measured clinically as residual.

Study limitations

The limitations belong to the underlying literature. Several influential observations rest on very small cohorts, including four patients for the quiescent stem-like population and its marker variability, and the original investigators state that validation in larger cohorts is required to determine general applicability [18,23]. Enrichment strategies differ between studies and are frequently patient-tailored, so the populations sequenced are not directly comparable [11,19]. Distinguishing malignant from normal cells relies on transcriptomic profile or on inferred mutation status, both of which carry error [12,19]. Cryopreservation and thawing alter transcriptional state, and most samples are banked rather than fresh [11,19]. And the paediatric resistance data derive from patients who achieved remission, so the cells characterised are those that survived in responders rather than in refractory disease [19].

Two gaps deserve naming. No study reviewed here establishes whether a marker set validated in one cohort identifies the relevant population in an unselected patient, which is what patient specificity would require testing [18,23]. And no clinical pathway exists for acting on a per-patient cellular composition, so the hierarchy frameworks remain descriptive rather than actionable [13,14].

Conclusion

Single-cell transcriptomic profiling has resolved six malignant cell states along the differentiation axis in acute myeloid leukaemia, with abundances varying strikingly between tumours, and has identified a quiescent stem-cell-like population carrying raised AP-1 transcription factors and reduced class II antigen presentation. Roughly half of leukaemic stem and progenitor populations express stem cell and oxidative phosphorylation signatures and tolerate chemotherapy preferentially. The most consequential finding is negative: the CD34-positive CD38-negative definition that has guided this field for nearly three decades contains normal haematopoietic stem cells while missing leukaemic ones outside the gate, and a marker upregulated in one of four patients suggests these

populations may be patient-specific. A universal stem-cell-directed therapy presupposes a universal target that the single-cell data do not yet support. The more promising route may not require one: resistant cells are defined by oxidative metabolism rather than by phenotype, and an agent targeting that state already exists.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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