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Single Cell Biology

Commentary

Role of Hematopoietic Stem Cell in Human Blood

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DESCRIPTION

Despite the fact that Hematopoietic Stem Cells (HSC) gives rise to a wide range of cell types in the blood system. We use Drop-seq, a massively parallel single-cell RNA sequencing (scRNA-seq) method, to profile 20,000 progenitor cells from human cord blood without prior enrichment or depletion for distinct lineages based on surface markers [1]. The transcriptional compendium of progenitor states in human cord blood, comprising four committed lineages downstream from HSC, as well as the transcriptional dynamics underpinning destiny commitment, are revealed in our findings [2]. We find intermediate stages that co-express "primed" programs for numerous downstream lineages at the same time, as well as significant heterogeneity in early molecular transitions between myeloid subsets. We demonstrate the molecular similarity between these two extensively used systems by combining our data with a newly released scRNA-seq dataset from human bone marrow. We next employ ATAC-seq to further investigate the chromatin dynamics of "primed" transcriptional programs. Finally, we show how Drop-seq data may be used to discover new heterogeneous cell state surface markers that correspond with functional output. Hematopoiesis is the dynamic process by which a single Hematopoietic Stem Cell (HSC) can give rise to the incredible cellular diversity found in blood, possibly representing tens to hundreds of different cell types that can be classified into the erythroid, myeloid and lymphoid lineages. Despite their importance in biology and medicine, the molecular pathways that cells take during lineage commitment are poorly understood. Individual HSCs lose pluripotency sequentially and pass through unique intermediate progenitors represented by a sequence of binary branchings, with the initial lineage decision indicating either myelo-erythroid or lymphoid specification, according to seminal experimental work in the rat. Recent studies, on the other hand, have proposed minor and major changes to the traditional model's structure, such as positing a direct path from HSC to erythroid and megakaryocytic lineages or demonstrating multiple lineage origins for myeloid cells, all highlighting a lack of consensus regarding the molecular nature of early hematopoiesis fate transitions. Fluorescence-Activated Cell Sorting (FACS) enrichment of Potential Progenitor Cell (PPC) populations is the primary source of evidence for each of these hypotheses (FACS). Slight variations in the surface markers used, the enrichment gating approach, or the downstream assay conditions can all distort the results and interpretation of these study. Furthermore, the techniques for identifying intermediate progenitor types can differ significantly between laboratories, necessitating unsupervised approaches to describe transition states at the single cell level [3,4]. This is especially true in human hematopoiesis, where well-studied rodent markers do not always translate to human systems. Single-cell RNA-seq (scRNA-seq), on the other hand, can provide a detailed molecular characterization of single cells that is an excellent complement to classic differentiation or FACS-based phenotyping methods. The routine characterization of thousands of single cells and the computer reconstruction of complex developmental processes have been facilitated by massively parallel techniques that barcode cells in early stages of library preparation [5]. Particular cells in this pool (which was depleted for the early progenitors expressing stem cell marker Sca-1) were largely committed to individual lineages, according to a massively parallel scRNA-seq study of thousands of myeloid-restricted cells from the mouse bone marrow. Furthermore, a ground breaking study of human bone marrow CD34+ cells that combined single-cell transcriptional and functional analysis highlighted the continuous nature of early hematopoietic differentiation and concluded that lineage commitment was not marked by distinct branching during early transitions.

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