Parallel bimodal single-cell sequencing of transcriptome and chromatin accessibility

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ABSTRACT

Joint profiling of transcriptome and chromatin accessibility within single cells allows for the deconstruction of the complex relationship between transcriptional states and upstream regulatory programs determining different cell fates. Here, we developed an automated method with high sensitivity, assay for single-cell transcriptome and accessibility regions (ASTAR-seq), for simultaneous measurement of whole-cell transcriptome and chromatin accessibility within the same single cell. To show the utility of ASTAR-seq, we profiled 384 mESCs under naive and primed pluripotent states as well as a two-cell like state, 424 human cells of various lineage origins (BJ, K562, JK1, and Jurkat), and 480 primary cord blood cells undergoing erythroblast differentiation. With the joint profiles, we configured the transcriptional and chromatin accessibility landscapes of discrete cell states, uncovered linked sets of cis-regulatory elements and target genes unique to each state, and constructed interactome and transcription factor (TF)–centered upstream regulatory networks for various cell states.

FIGURE

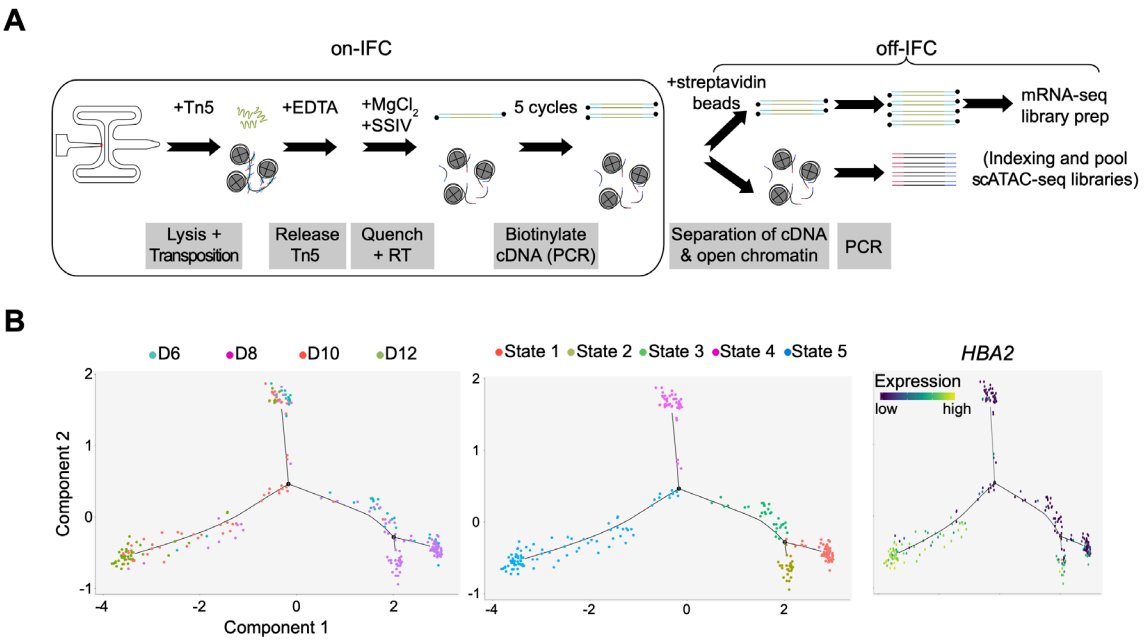

FIGURE LEGEND

(A) Overview of the multi-modal single-cell technique, ASTAR-seq (Assay for Single-cell Transcriptome and Accessibility Regions).

(B) Left: trajectory of erythroblast differentiation identified from ASTAR RNA-seq libraries using DDRTree dimension reduction. Colors represent time-points. Middle: Trajectory plot revealing the pseudotemporal states. Colors represent pseudotemporal states. Right: Superimposition of *HBA2* expression on the trajectory. Colors represent expression levels.