Diversification of reprogramming trajectories revealed by parallel single-cell transcriptome and chromatin accessibility sequencing

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ABSTRACT

Cellular reprogramming suffers from low efficiency especially for the human cells. To deconstruct the heterogeneity and unravel the mechanisms for successful reprogramming, we adopted single-cell RNA sequencing (scRNA-Seq) and single-cell assay for transposase-accessible chromatin (scATAC-Seq) to profile reprogramming cells across various time points. Our analysis revealed that reprogramming cells proceed in an asynchronous trajectory and diversify into heterogeneous subpopulations. We identified fluorescent probes and surface markers to enrich for the early reprogrammed human cells. Furthermore, combinatory usage of the surface markers enabled the fine segregation of the early-intermediate cells with diverse reprogramming propensities. scATAC-Seq analysis further uncovered the genomic partitions and transcription factors responsible for the regulatory phasing of reprogramming process. Binary choice between a FOSL1 and a TEAD4-centric regulatory network determines the outcome of a successful reprogramming. Together, our study illuminates the multitude of diverse routes transversed by individual reprogramming cells and presents an integrative roadmap for identifying the mechanistic part list of the reprogramming machinery.

FIGURE

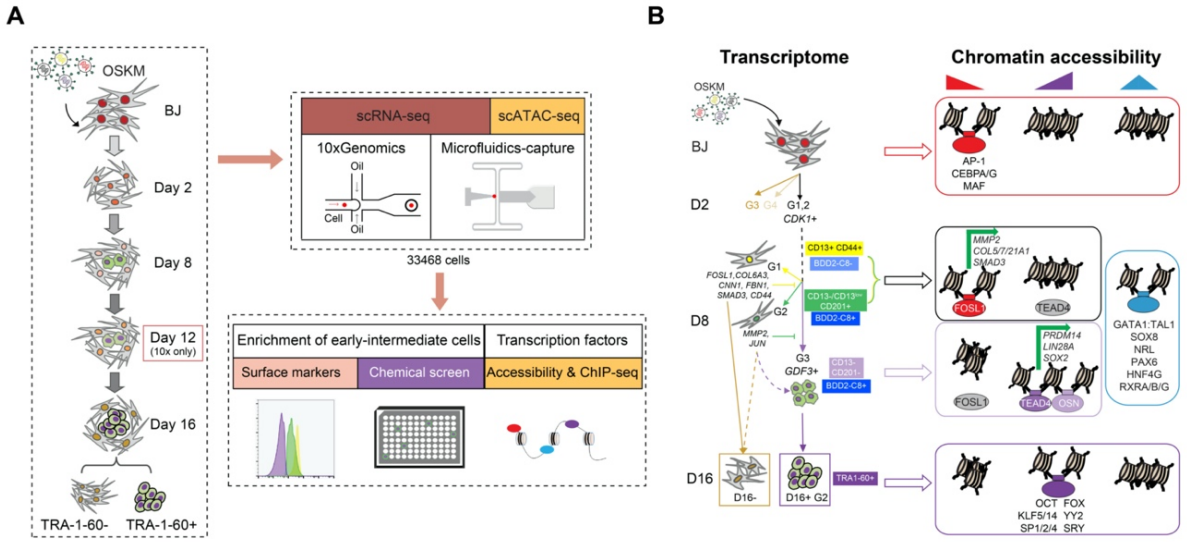

FIGURE LEGEND

(A) Overview of the prepared single-cell NGS libraries across various time points of human cellular reprogramming. The microfluidic platform was used to prepare 439 scRNA-Seq and 891 scATAC-Seq libraries (duplicates) of good quality. 10X Genomics platform was utilized to prepare 32,138 scRNA-Seq libraries of good quality.

(B) Proposed model of the study.