cell-cycle signature could affect high-dimensional distances between cells in a way that obscures their segregation by lineage-specific genes, we attempted to remove it[37]. Specifically, we filtered from the analysis genes that were significantly correlated with the sum Z-score of G2/M genes ($P < 10^{-4}$, Bonferroni corrected; 401 genes total, resulting in 28,205 remaining genes). PCA and clustering analysis were repeated using the reduced gene list.

Clustering of single-cell profiles. We performed unsupervised clustering of the processed single-cell data with the Louvain–Jaccard method package from ref. 38. To assess cluster stability and choose the value of k, we downsampled 85% of cells and applied the Louvain–Jaccard method using 50 principal components. We tested k values from 10 to 30 and for each k we compared 100 times the randomly downsampled clustering using the Jaccard-index measurement in the R package fpc (Flexible Procedures for Clustering). We considered a Jaccard-index minimum of 0.75 as sufficiently robust and selected values of $k > 30$, which resulted in the identification of 11–12 clusters[39]. Differential expression analysis was performed using the method package from ref. 38 (results are included in Supplementary Table 2).

Data availability. The Gene Expression Omnibus accession number is GSE90742. Additional data files will be made available upon reasonable request from the corresponding author. SPRING plots (with and without removal of the G2/M cell-cycle signature) are available for inspection at the following links: https://kleintools.hms.harvard.edu/tools/springViewer.html?cgi-bin/client_datasets/ARF2017_combined_nocycle and https://kleintools.hms.harvard.edu/tools/springViewer.html?cgi-bin/client_datasets/ARF2017_combined.

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