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Self-supervised deep learning enables label-free high-dimensional morphology profiling of immune cell types

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Key points

- High-dimensional morphology information represents a novel modality to describe cell morphology and complex cell biology processes.
- The REM-I platform combines label-free brightfield imaging, deep learning, morphometrics, and gentle cell sorting to leverage high-dimensional single cell morphology as a biological readout, eliminating the need for specific biomarkers.
- Applications include high-throughput sample characterization, disease detection/enrichment, drug/functional screening, and multi-omic integration.
- Here, we demonstrate that the Deepcell **H**uman **F**oundation **M**odel (HFM) using high-dimensional morphology of different immune cells identified distinct morphotypes associated with subpopulation of PBMC, human stem cells, and other immune cells.

Introduction

- Morphology is a fundamental cell property associated with identity, state, & function, but there is a need for high-dimensional, unbiased, & quantitative assessment.
- The Deepcell REM-I platform enables high-dimensional morphology analysis and enrichment of unlabeled single cells using artificial intelligence (AI), advanced imaging, and microfluidics, enabling high resolution profiling of population heterogeneity.
- Deepcell's Human Foundation Model (HFM) is a hybrid architecture that combines self-supervised learning and morphometrics (computer vision) to extract 115 dimensional embedding vectors representing cell morphology from high-resolution REM-I cell images.

Methods

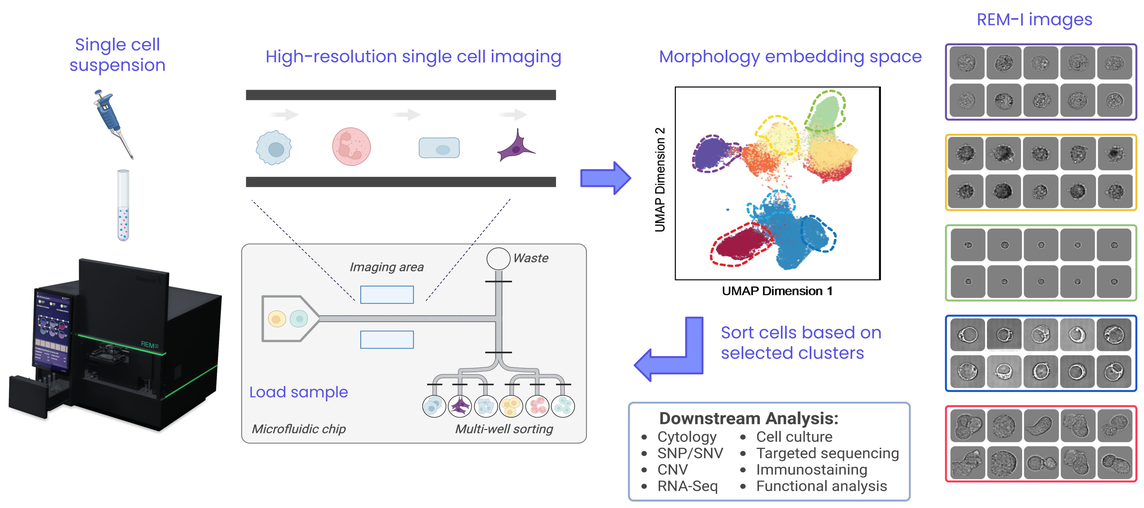

Figure 1. The REM-I workflow. A single cell suspension is loaded onto a microfluidic chip where bright-field images of single cells are captured and analyzed in real-time by our HFM. High-dimensional morphological features are visualized by UMAP, and user-defined cell clusters can be sorted for downstream functional or molecular analysis. Morphology embeddings are used to profile the morphological heterogeneity of the cells, identify which morphology features differentiate each condition, and train a random forest classifier to predict each class of cells.

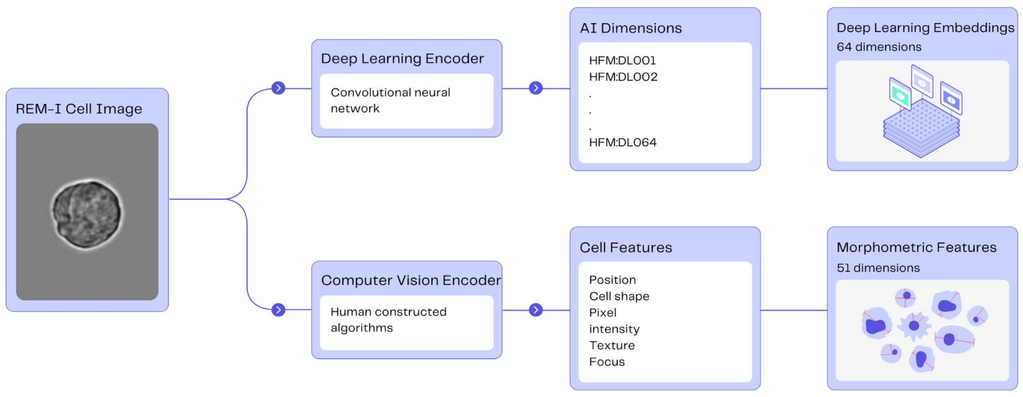

Figure 2. The Human Foundation Model (HFM) is a feature extractor. Features of cell images are encoded into multi-dimensional numerical vectors. HFM contains 115 combined embedding dimensions, including 64 deep learning derived embeddings and 51 computer vision derived morphometrics, including cell size, shape, texture, and intensity, as well as biological features such as blebbing and pigmentation.

Results

I. PBMC

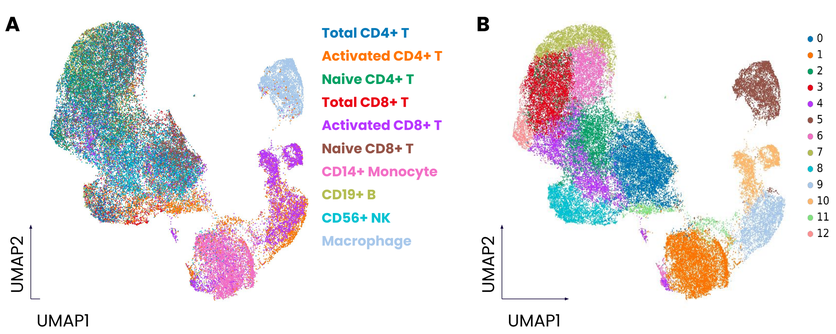

Figure 3. Morphology UMAP of immune cells residing in PBMC samples. Profiled patient-derived whole PBMC samples and purified immune subsets were imaged on the REM-I platform and analyzed with dimensionality reduction techniques to generate morphology UMAP colored by **(A)** cell type and **(B)** Leiden clustering.

Results continued

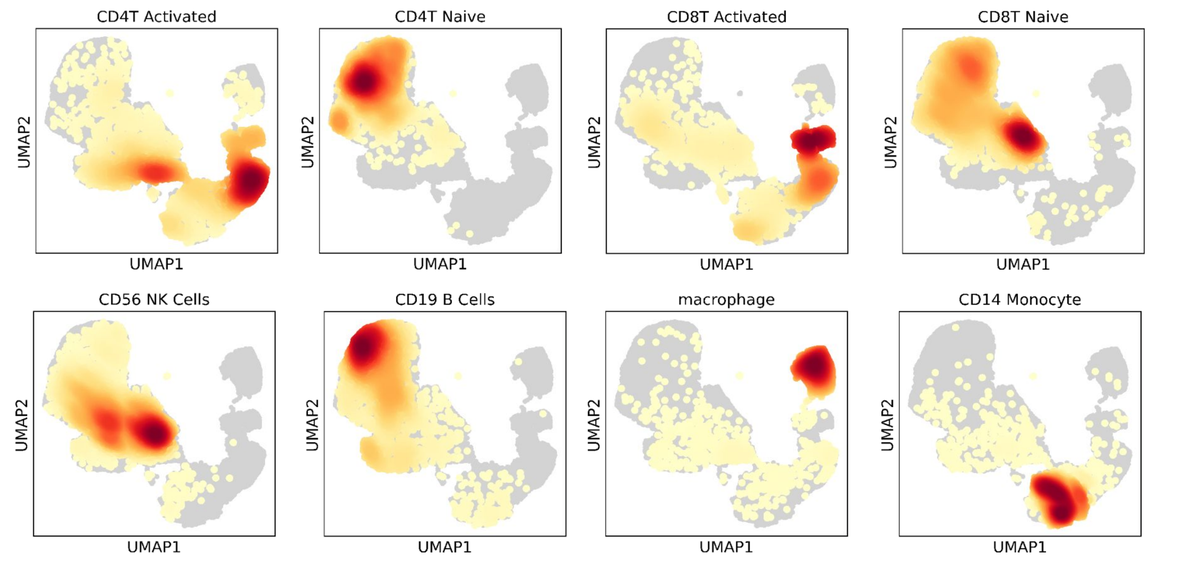

Figure 4. Density UMAP plots show unique morphotypes for each PBMC subset. Embeddings extracted from images of cells derived from multiple donors are shown (n≥3). Each cell subtype occupies a specific region of the total PBMC background (grey) according to the morphologic features.

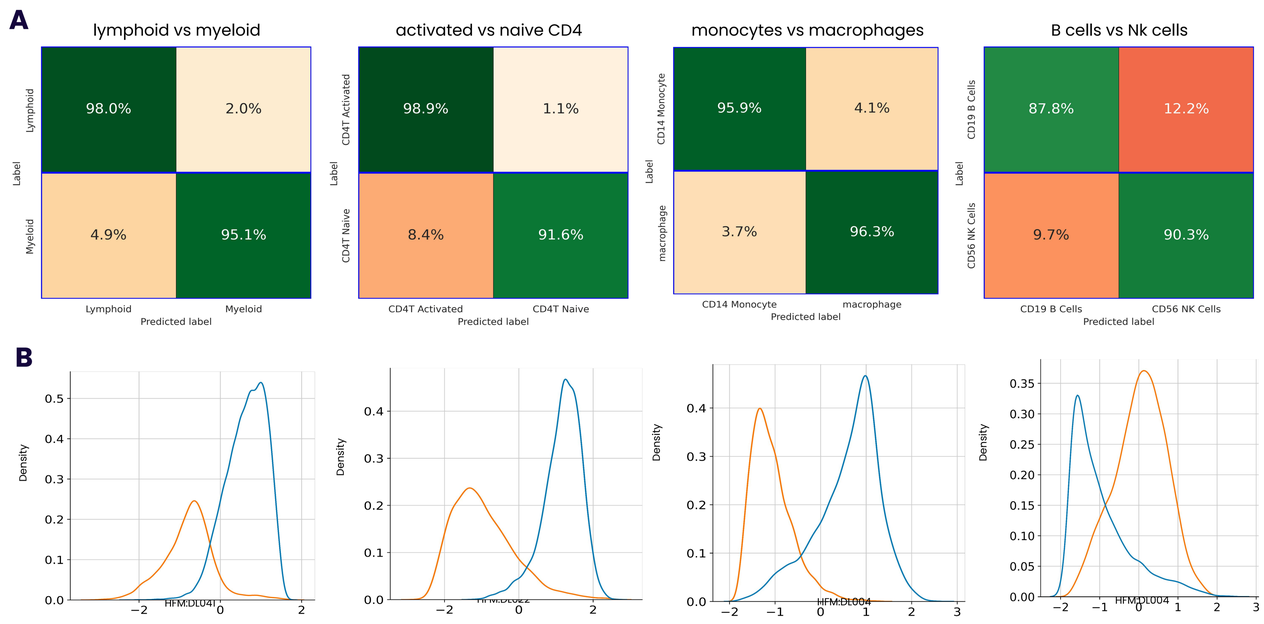

Figure 5. Cell lineage classification performance using our Human Foundation model (HFM) (A) Confusion matrices: HFM predicts cell lineage. **(B)** Density plots of top HFM deep learning features. Using both, AI and computer vision features enhances model explainability and enables biological interpretation.

II. Stem cells

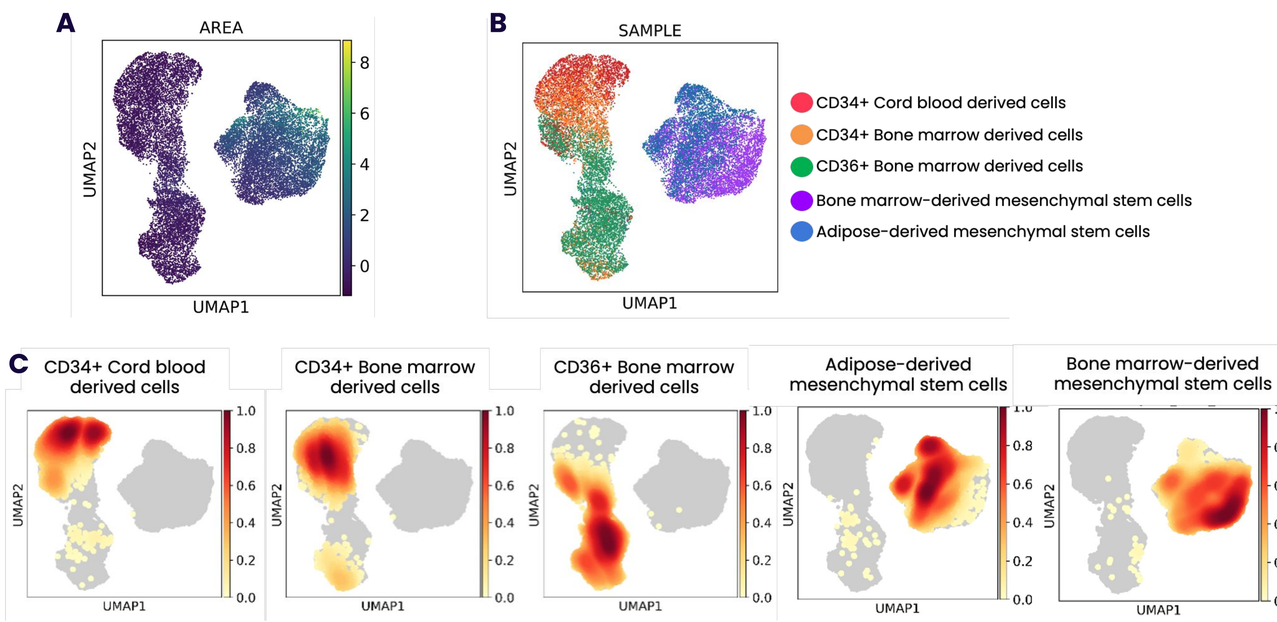

Figure 6. Adult Stem cells. (A) Area clustering using morphometric features. **(B)** Sample morphology UMAP with 115 deep learning and morphometric features reduced to 2 dimensions shows distinct clustering patterns of the different stem cell types. **(C)** Density plots showing the unique clustering of CD34+ hematopoietic stem cells and CD36+ erythroid progenitor cells, as well as mesenchymal stem cells derived from adipose tissue and bone marrow.

Conclusions

- These results suggest that high-dimensional morphology can be used to characterize phenotypes in a label-free manner, and provide new insights into cell biology.
- Functionally distinct cells can be separated from one another with high-dimensional morphology in AI and morphometric embedding space.
- The REM-I platform combines label-free imaging, deep learning, computer vision, and gentle cell sorting to harness high-dimensional single cell morphology as a biological readout.

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