Integrating morphology and scRNA-Seq to characterize cellular heterogeneity

Deepcell

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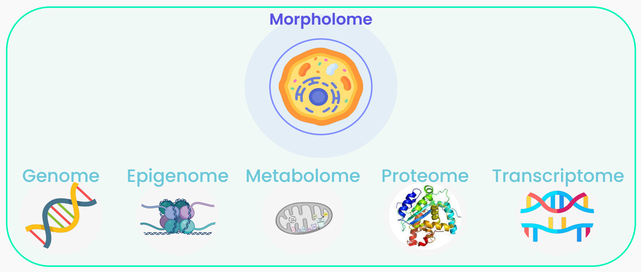
KEY POINTS

- The REM-I platform performs real-time deep learning interpretations of cell morphology.
- High-dimensional morphology profiling shows high concordance with cell images, gene expression profiles, flow cytometry, and genomic sequencing.
- High-dimensional morphology information represents a novel modality to describe cell morphology and complex cell biology processes.

INTRODUCTION

- Morphology is a fundamental cell property associated with identity, state, & function, but there is a need for high-dimensional, unbiased, & quantitative assessment.
- Single cell high-dimensional morphology analysis on the REM-I platform provides a deeper assessment of heterogeneity by augmenting classical single cell multi-omics data (mRNA, genome, chromatin accessibility, protein).



METHODS

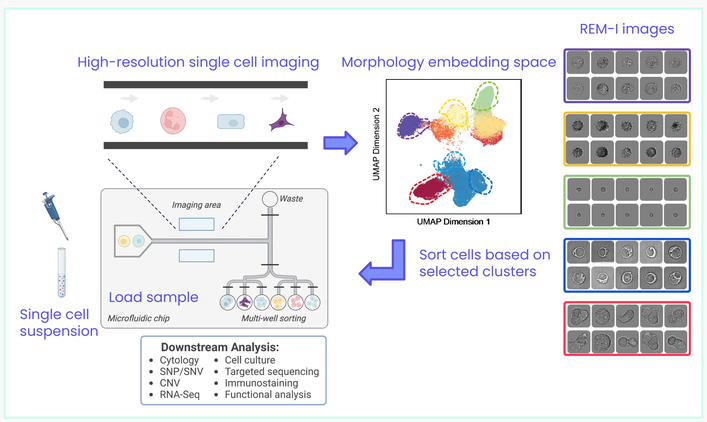


Figure 1. The REM-I workflow. A single cell suspension is loaded onto a microfluidic chip where images of single cells are captured and analyzed in real-time by the Human Foundation Model. High-dimensional morphological features are visualized by UMAP, and user-defined cell clusters can be sorted for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

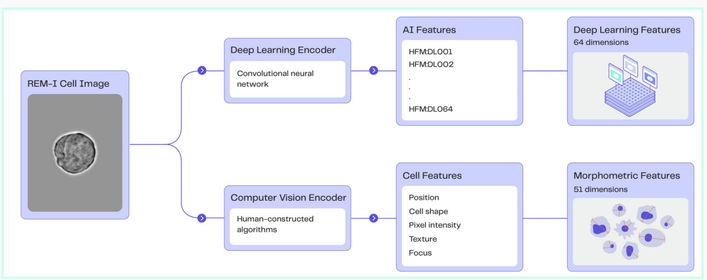


Figure 2. HFM is a feature extractor. Features of cell images are encoded into multi-dimensional numerical vectors.

RESULTS

High-dimensional morphology UMAP visualization

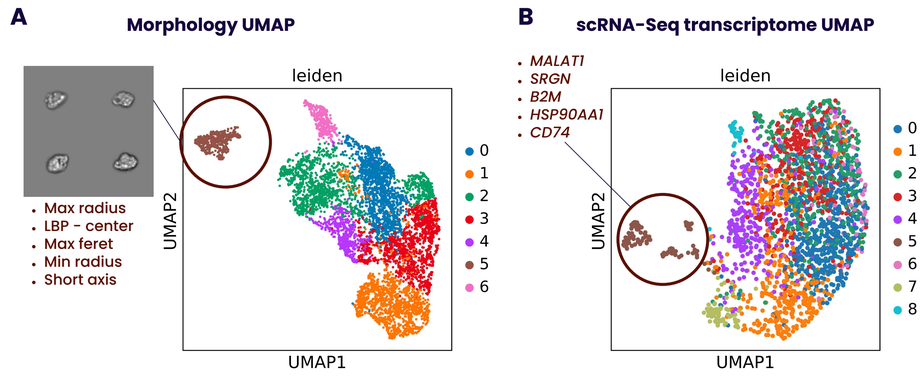
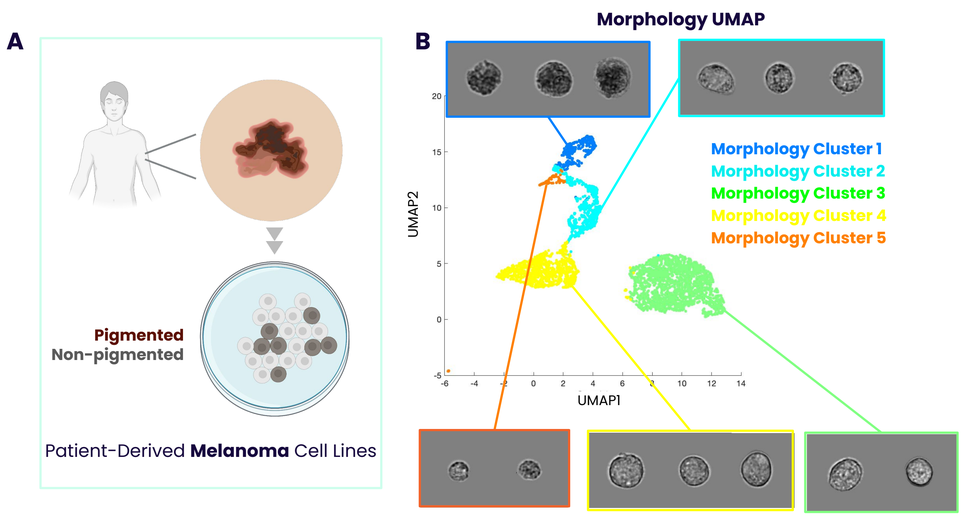


Figure 3. Dimensionality reduction methods applied to morphological profiling. (A) Morphology UMAP with 115 deep learning and morphometric features reduced to 2 dimensions shows distinct clustering patterns, with leiden cluster 5 being highly differentiated from other clusters. LBP; local binary pattern. **(B)** scRNA-Seq UMAP of the same sample shows a similar outlier group. UMAP visualization from both high-dimensional morphological and transcriptomic modalities can be interpreted in the same way.

Morphology clusters display unique gene expression profiles in patient-derived melanoma cell line



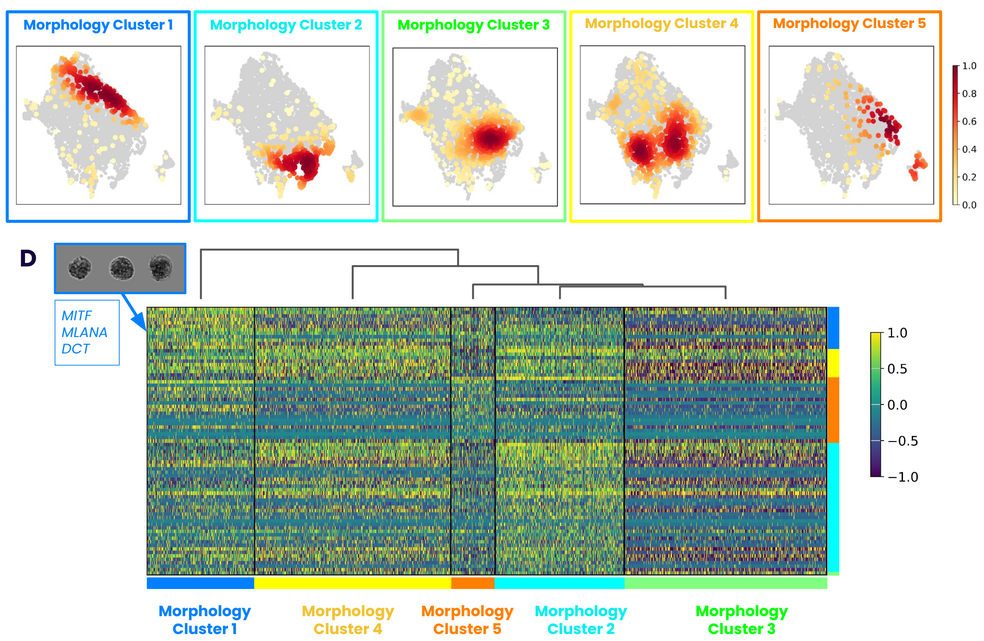
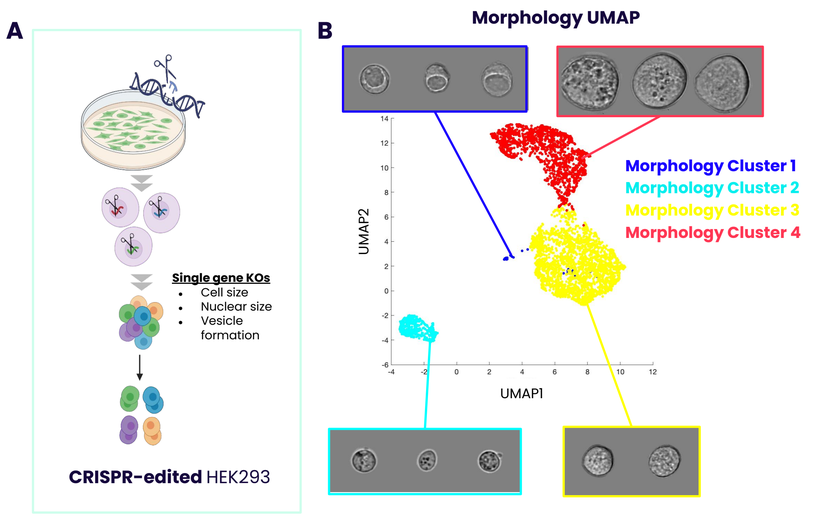


Figure 4. scRNA-Seq gene expression profiling of morphology clusters. (A) Patient-derived melanoma cells were imaged on the REM-I platform. **(B)** The resulting morphology UMAP showed 5 cell groups with distinct morphological features, which were sorted for downstream **(C)** scRNA-Seq analysis. Results showed sorted morphology clusters display differential gene expression patterns, indicating cell groups defined by high-dimensional morphology profiling reflect distinct cell identities. **(D)** Of note, Cluster 1 shows enrichment of pigmented cells, as confirmed by representative brightfield images and increased relative gene expression of the melanin biosynthesis pathway.

RESULTS cont.

Morphology profiling reveals large shifts associated with single gene KOs



Single gene KOs result in large morphology changes not detected in gene expression

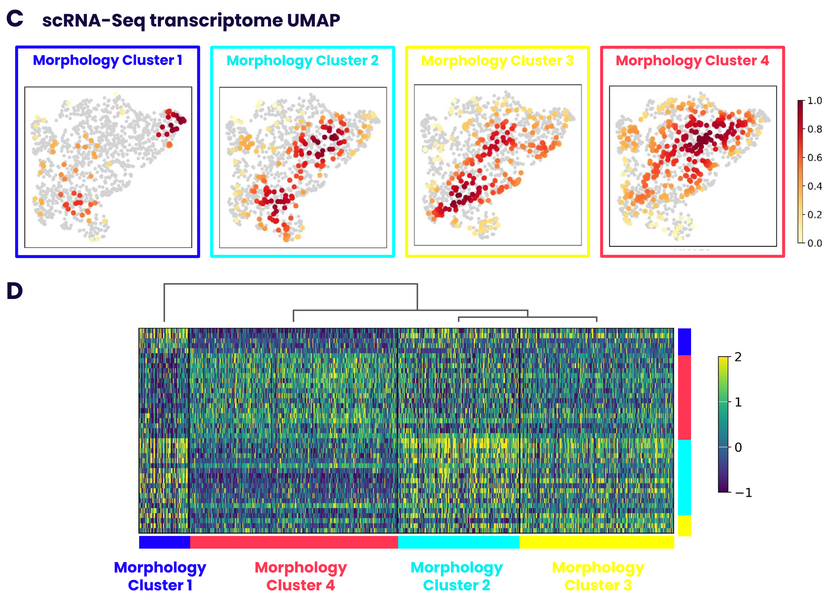


Figure 5. Morphology profiling of CRISPR-edited HEK293 cell lines. (A) 11 genes were chosen based on reported effects on vesicle formation, cell size, and nuclear size and individual CRISPR-edited HEK293 cells lines were generated for each selected gene. **(B)** KO cell lines were imaged on the REM-I platform and high-dimensional morphology analysis showed 4 distinct cell groups. Representative images illustrate effect on cell size and vesicle formation. **(C)** scRNA-Seq analysis of morphology clusters showed gene expression changes corresponding to large shifts in morphological profiles of cells. **(D)** Sorted morphology clusters exhibit distinct transcriptional programs, especially Clusters 1 and 4, that may be driven by shifts in morphological traits.

CONCLUSIONS

- High dimensional morphology profiling can be interpreted in the same way as other single cell visualization techniques (Fig. 3)
- In heterogeneous samples, single cell morphology profiling can complement characterization of cells as an orthogonal biological readout (Fig. 4-5)
- High-dimensional morphological characterization with the REM-I platform can provide meaningful phenotypic information on cells that are minimally segregated in transcriptional space

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