

Size-based tissue decoupling and in vitro reconstitution for tumor-immune microenvironment modeling on a microfluidic chip

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Abstract

Tumor microenvironment (TME) consists of multiple cell types including cancer cells, cancer-associated fibroblasts (CAFs) and various immune cells. However, conventional in vitro tumor models include cancer cells alone or non-paired cancer cells and stromal cells, failing to recapitulate the cellular complexity of patient TME. Here, we present the microfluidic device that enables the simultaneous isolation of three key TME components - cancer cells, CAFs and immune cells - from a patient tumor tissue using gravity-driven flow and porous membranes. Unlike previous methods that isolate only one or two cell types, our device ensures efficient and reproducible separation while preserving patient-specific characteristics. Notably, the isolated cancer cells successfully formed organoids, which retained their original histological architecture, as confirmed by H&E staining. Additionally, the isolated CAFs exhibited distinct inter-patient phenotypic heterogeneity. The isolated immune cells contains both CD4 and CD8 T-cells, which play a crucial role in anti-tumor immune responses. Using these three components, we successfully reconstituted patient-specific TME models on a microfluidic chip, allowing for a controlled and physiologically relevant study of tumor-stromal interactions. This platform provides a valuable tool for investigating tumor heterogeneity and cell-cell interactions with significant implications for personalized/precision tumor modeling and therapeutic development.

Results

Figure 1. Size-based cell decoupling in microfluidic device using capillary flow and characterization of decoupled cells.

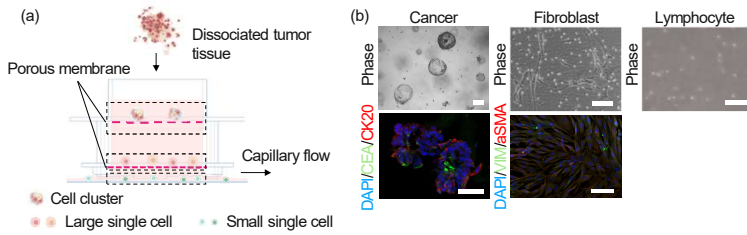


Figure 2. Bottom surface wettability modification enhances capillary flow in the lower decoupling device.

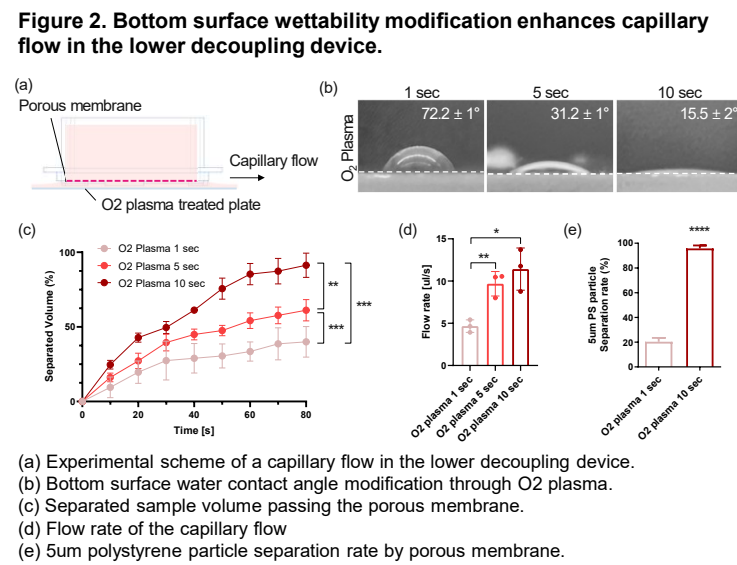
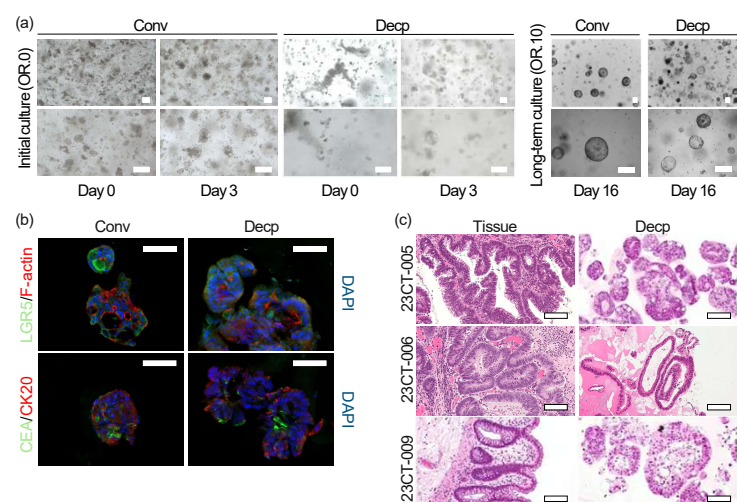


Figure 3. Phenotypic characterization of decoupled cells reveals preservation of cell type-specific features



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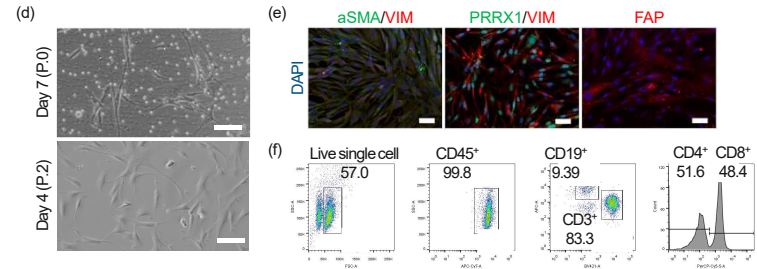


Figure 4. CAF enhances in vitro recapitulation of patient tumor tissue architecture and cancer phenotype

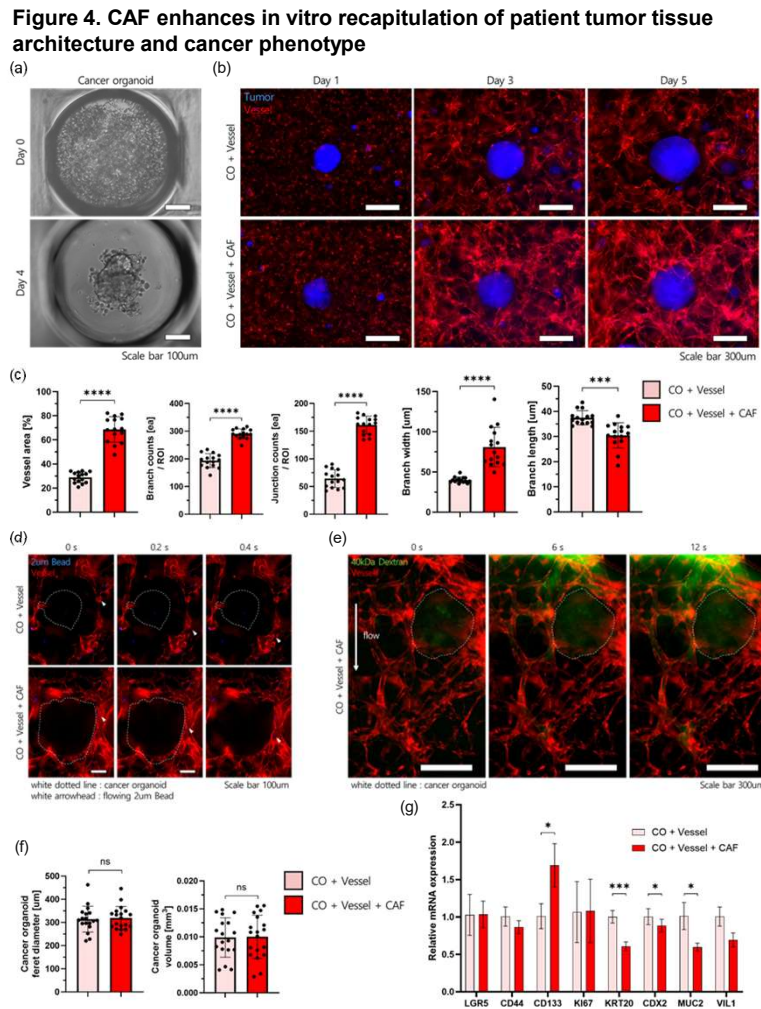


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