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Patient-derived micro-organospheres (MOS) recapitulate tumor microenvironment and heterogeneity for precision oncology

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Background

Preclinical models that can recapitulate patients' intra-tumoral heterogeneity and microenvironment are crucial for tumor biology research and drug discovery. In particular, the ability to retain immune and other stromal cells in the microenvironment is vital for the development of immuno-oncology assays. However, current patient-derived organoid (PDO) models are largely devoid of immune components.

Methods

We first developed an automated microfluidic and membrane platform that can generate tens of thousands of micro-organospheres (MOS) from resected or biopsied clinical tumor specimens within an hour. We next characterized growth rate and drug response of MOS. Finally, extensive single-cell RNA-seq profiling were performed on both MOS and original tumor samples from lung, ovarian, kidney, and breast cancer patients.

Results

MOS derived from clinical tumor samples preserved all original tumor and stromal cells, including fibroblasts and all immune cell types. Single-cell analysis revealed that unsupervised clustering of tumor and non-tumor cells were identical between original tumors and the derived MOS. Quantification showed similar cell composition and percentages for all cell types and also preserved functional intra-tumoral heterogeneity. An automated, end-to-end, high-throughput drug screening pipeline demonstrated that matched peripheral blood mononuclear cells (PBMCs) from the same patient added to MOS can be used to assess the efficacy of immunotherapy moieties.

Conclusions

Micro-organospheres are a rapid and scalable platform to preserve patient tumor microenvironment and heterogeneity. This platform will be useful for precision oncology, drug discovery, and immunotherapy development.

Legal entity responsible for the study

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