Assessing efficacy therapies in human colorectal cancer organoids using a standardized screening workflow

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BACKGROUND

Precision medicine for cancer patients promises the tailoring of targeted therapies to specific genetic alterations. Still, the majority of cancer patients lack efficient targeted therapy options with lasting benefit. Ex vivo assays, such as tumor tissue explants, hold the promise to directly measure the impact of anti-cancer compounds and their combinations. A significant challenge for ex vivo drug testing lies in the efficient establishment of fresh primary cell cultures for testing, within clinically actionable timeframe, and in the available tumor volume. To this end, patient-derived organoids (PDOs) have been proposed as viable and efficient alternatives for ex vivo testing. PDOs show long-term expansion potential while retaining tumor histopathology as well as cancer gene mutations. We have shown how homogenous reproducible PDOs based on Gri3D® hydrogel microwell arrays can be generated for high-throughput drug testing of single and combination therapies. Here we identify on human colorectal cancer organoids the optimal targeted treatment option for a given patient. We also show that by targeting pathways in a combinatorial approach, a lower therapeutic dosage of each individual drug is required, potentially also reducing toxic side effects.

METHODS

Patient-derived organoids from the needle biopsy of one patient were generated in Gri3D® 96WP imaging-bottom 500 μm microwells and exposed to anti-cancer drugs. All steps of the screen were executed by an automated liquid handling system: hydrogel calibration, cell seeding, medium changes, drug exposure and readout using image-based Live/Dead assay. Organoids were segmented and fluorescence data were analyzed using Doppl’s automated toxicity assessment pipeline to accurately quantify the degree of cytotoxicity.

RESULTS

A single-drug dose response screen was performed on PDOs (N=2). Organoids treated with MEK1/2 inhibitor Trametinib showed high cytotoxicity starting at 1 μM. Cytotoxicity was detected for Regorafenib and Palbociclib from 10 μM, while Olaparib only induced cytotoxicity at high dose (Fig. 1). Regorafenib and Trametinib both induced a dose-dependent reduction in organoid proliferation (Fig. 1). Trametinib was tested in combination with the four other drugs to assess whether its efficacy could be enhanced. Indeed, its addition to cyclin-dependent kinase inhibitor Palbociclib revealed toxicity and decreased organoid proliferation at Trametinib 0.5 μM and Palbociclib 5 μM, two doses that were non-toxic when used alone (Fig. 2).

CONCLUSIONS

• The use of Gri3D® 96 500 μm microwells allows the generation of more than 70 organoids per well, which are segmented for high-content image analyses in a single field of view.
• Our findings are amongst the first reporting a personalized medicine approach using PDOs for combination therapies assessment.
• Combination therapies allow a reduction of secondary effects by lowering doses of the single agents, while avoiding resistance.
• Future developments will focus on expanding our organoid patient pool and comparing the organoid results to clinical outcomes.

REFERENCES


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