B-10

Development of GEP-NEN Patient Derived Organoids for Long Term Culture and Therapy Screening

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BACKGROUND

Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs) are a rare subset of cancers which nevertheless are a rising health burden. Development of new therapies suffers from several bottlenecks, including low patient accrual and poor understanding of tumor characteristics. Patient tumor organoids (PTOs) are a novel model capable of improving screening of patient tissue in an accurate, standardized, and high-throughput capacity. In this study, we utilized patient tumors for creation of high-fidelity PTOs from a variety of GEP-NENs.

METHODS

Tumors from patients undergoing clinically guided surgeries were processed within two hours of resection and dissociated into single-cell suspension. Cells were encapsulated into Matrigel and cultured into two groups. The first group was grown for 10 days and assessed for viability then treated with a panel of clinically approved and investigational therapies. The second group was grown for long-term expansion and biobanking, followed by characterization using immunohistochemistry for chromogranin A, synaptophysin, and ki67 and genetic profiling at passages 0, 3, and 6 to ensure tumor cell maintenance.

RESULTS

From March 2023-July 2024, thirty patients provided 69 tumors for PTO development. These included small intestine (n=10), pancreatic (n=19), and gastric (n=1) neuroendocrine tumors derived from both primary and metastatic origins. Ongoing short-term culture (^{3}3 passages) was successful for 51/69 (74%) of specimens while long term culture (^{3}6 passages) was successful in 18/69 (26%) of specimens, with an average passage time of 3-4 weeks. Passaging time and number was significantly correlated with tumor grade, with grade 2 and 3 organoids capable of more and faster passages. PTOs maintained immunohistochemical characteristics of the parent tumor types including neuroendocrine tumor cell markers and grade and demonstrated similar genetic profiles across passages. Early-stage therapeutic screening was successfully performed for 52/55 (95%) tumors, demonstrating dose-dependent and clinically dose relevant sensitivity towards chemotherapy and small molecule inhibitor therapies including capecitabine:temozolomide, everolimus, cabozantinib and sunitinib. Treatment efficacy could also be stratified based on origin and tumor grade, with higher grade tumors more sensitive to

chemotherapy regimens when compared to lower grade tumors. Finally, PTOs responded based on VHL mutation status to Belzutifan and demonstrated resistance towards previously deployed clinical regimens.

CONCLUSIONS

Development of GEP-NEN PTOs is feasible for standard of care therapy testing. The establishment of large-scale prospective clinical PTO cohorts will allow integration of molecular biological characteristics and immediate treatment responses in cancer patients, reducing the time of the clinic-bench-clinic cycle, and thus help develop a platform for personalized oncology therapy.

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