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Patient-Derived Organoids and Their Potential for Precision Medicine in Neuroendocrine Tumors

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BACKGROUND

Neuroendocrine tumors (NETs) are a heterogeneous group of malignant neoplasms arising from neuroendocrine cells distributed throughout the body. The most common sites of NETs are the gastrointestinal tract, pancreas and lungs. The clinical management of NETs is not standardized, with few FDA-approved therapies. Moreover, drug development has been challenging for NETs due to limited pre-clinical models. To address this unmet need, the NCI Natural History Study of Children and Adults with Neuroendocrine Neoplasms (NCT03739827 and NCT05237934) aims to develop preclinical models, such as *in vitro* 3-dimentional tissue organoids, to develop more personalized therapies for NET patients.

METHODS

From February 2020 – July 2022, 17 surgical specimens were collected for the development of patient-derived organoids. We selected 3 NET organoids (NET16, NET17 and NET18) to test the activity of select drugs: dovitinib (VEGFR inhibitor), vistusertib (mTOR inhibitor), cobimetinib (mitogen-activated protein kinase 1 inhibitor) and TAK243 (ubiquitin activating enzyme inhibitor). NET16 was derived from a 72-year-old male with a grade 1 (Ki-67 <3%) small bowel NET. NET17 was derived from a 36-year-old female with grade 2 liver segment metastasis. NET 18 was derived from a 66-year-old male, with grade 2 (Ki-67=3%) liver segment metastasis. Cell viability assays were performed using Cell Titer Glo after 3 days of drug testing. Chromogranin A, synaptophysin, and Ki67 biomarkers will be assessed in the parental tissues as well as the organoids.

RESULTS

Overall, the activity of the drugs tested was significantly higher in NET16 than NET17 and NET18. TAK243 was the most potent drug in both NETs but had a greater effect in NET16 (IC50=0.39 nM) than NET17 (IC50=43.17 nM) and NET18 (IC50=6.02 nM). Dovitinib and vistusertib were more potent in NET16 (dovitinib IC50=1.46 µM; vistusertib IC50=0.17 µM) than NET17 (dovitinib IC50=11.18 µM; vistusertib IC50=16.45 µM) and NET18 (dovitinib IC50=9.36 µM; vistusertib IC50=7.77 µM). Cobimetinib had modest activity in NET 17 (IC50=12.02 µM) and NET18 (IC50=13.39 µM).

CONCLUSIONS

We have developed an assay for *in vitro* drug testing in well-differentiated patient-derived NET organoids that will allow for further, large scale drug screening to help predict patient drug responses. Tumor heterogeneity may be contributing to the differences seen in the drug response between the three NET organoids and requires further evaluation. Replication of these studies in a larger subset of patient samples and drug combination studies will be important for the advancement of therapeutics in NETs.

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