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Use of patient-derived pre-clinical models to identify new and effective treatments for neuroendocrine tumors

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BACKGROUND

Neuroendocrine tumors (NETs) arise in different organs and are heterogeneous with limited treatment options. Preclinical models established from patient tumor specimens enable precision oncology by assessing the response to various drug treatments. Herein, we aim to develop patient-derived organoids (PDOs) and xenografts (PDXs) for NETs and use them to identify new treatment approaches.

METHODS

We established two pre-clinical models: patient-derived organoids (PDOs) and patient-derived xenografts ex-ovo (PDXovo), using fresh surgical samples from patients with gastroenteropancreatic NETs. To establish PDOs, the fresh tumor tissue sample is disassociated in single-cell suspension, and the cells are seeded in 384-well plates coated with chemically defined hydrogel. To assess the PDOs' progression and drug response, we use Chromalive™ non-toxic dyes to monitor the organoids' metabolic state, ER stress, and apoptosis. High-content imaging of the PDOs is done using an automated spinning disk confocal microscope (Opera Phenix, Revvity), and the image analysis uses customized algorithms. To establish NET patient-derived xenograft ex-ovo (PDXovo) models, we engraft small tumor tissue fragments into the chorioallantoic membrane of avian embryos. High-frequency ultrasound imaging (HF-US) is used to measure changes in tumor volume and vascularity. PDXovos are harvested and characterized at the endpoint using immunostaining and molecular biology approaches.

RESULTS

PDOs and PDXovos were established with a success rate of >95% and a take rate of >90%, respectively. We used NET PDOs from primary tumors (small intestine, pancreas, and cecum) and metastases (liver, lymph node) for high-throughput drug screening of clinically approved drugs alone and in combination with therapies currently used for GEP-NET. We have identified BH3-mimetics that inhibit anti-apoptosis proteins and augment the efficacy of clinically approved therapies for NETs.

We established over 160 PDXovos originating from 21 primary tumors and metastases. HF-US scanning of the PDXovos revealed successful tumor growth and vascularization. PDXovos were immunostained for neuroendocrine markers, such as chromogranin A, and markers of proliferation and apoptosis. We found that PDXovos resemble the tumor architecture and morphology of the corresponding patient tumor sample. We are currently evaluating the efficacy of the BH3-mimetics drug combinations using the PDXovo models to corroborate our findings further.

CONCLUSIONS

Overall, this study showed that we can reproducibly derive NET preclinical models on a large scale. Moreover, we have identified a new class of drugs for NETs, which we are further evaluating. Utilizing the dual approach of PDOs/PDXovo preclinical models will enable us to identify new potential treatments for patients with NETs.

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