B-20

Establishment of novel PDXovo models for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs)

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BACKGROUND

Neuroendocrine cancers arise in the endocrine cells localized throughout the body. Most are found in the Gastroenteropancreatic (GEP) system pancreas, stomach, and small and large intestines. They are heterogenous in their etiology, morphology, and phenotypes. Due to late diagnosis and low prevalence, clinical specimens are limited for research. Thus, preclinical models are pivotal for the understanding of this disease. This study focuses on establishing a novel patient-derived xenograft (PDX) model for GEP neuroendocrine neoplasm (GEP-NEN) known as PDX*ovo*. Our group has already shown that the PDX*ovo* model can be utilized in disease modeling and drug screening of numerous other cancers. Thus, we hypothesize that the PDX*ovo* system is an alternative approach to recapitulate the disease phenotype of GEP-NEN.

METHODS

For this study, patients were enrolled with informed consent, and fresh tissue samples (blood, tumor (primary and metastasis)) were collected by medical oncologists and surgical oncologists at the Susan Leslie Clinic for Neuroendocrine Tumors at the Odette Cancer Centre (OCC) at Sunnybrook Hospital. Part of the obtained tissue samples was stored in the OCC biobank, and the rest were diverted to the PDXcore facility at our institution.

RESULTS

Using fragments from freshly resected human small intestinal NEN specimens (primary and metastases), we were able to establish NEN PDX*ovos* with a take-rate of >90%. Ultrasound images revealed successful tumor formation and increased vascularity. Fragments of the PDX*ovos* were fixed for histological or cryopreserved for subsequent RNA and protein analysis. The PDX*ovos* are characterized by immunostaining for tumor-specific neuroendocrine (chromogranin and the somatostatin receptor SSTR2) and other microenvironment makers. We plan to examine the response of the PDX*ovos* to various treatments, such as the antiangiogenic inhibitor sunitinib, the mTOR inhibitor everolimus, and the immune checkpoint inhibitor anti-PD-1 antibody, and combinations thereof.

CONCLUSIONS

The significance of the findings of this study by far is the establishment of the PDX*ovo* model for GEP-NEN for the first time. PDX*ovos* is more cost-effective, fast, convenient, and widely available than conventional mice experiments. Upon further validation, this will guide successful future clinical trials in GEP-NEN patients.

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