Organoid models of hereditary and sporadic pheochromocytoma

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Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine-secreting neuroendocrine tumors known for their high heritability and genetic diversity that is reflected in discrete molecular subgroups. Metastatic and recurrent PPGLs have few therapeutic options, in part due to the lack of appropriate study models. Here, we report progress on the establishment of viable organoids from n=6 distinct pheochromocytomas, including hereditary (*VHL*) and sporadic tumors, and their histological, molecular, biochemical, functional, genomic and drug response characterization.
The six pheochromocytomas were obtained from patients with distinct clinical history and diverse ethnic background. Viable organoid cultures were successfully generated using fresh and processed frozen surgical material. Organoids were developed in a format compatible with histologic characterization and high-throughput drug screening. We observed cellular diversity with immunohistochemical expression of the neuroendocrine marker chromogranin A (n=6/6), sustentacular cell marker S100 (n=5/6, matching primary tumor pattern), and vascular marker CD34 (n=3/3). Five samples were developed into short and long-term cultures. Catecholamines and metanephrines were detected by LC-MS/MS in the media and matched the primary tumor pattern, suggesting that these organoid models are functionally active for at least one month. We also evaluated the response of tumor organoids from six PPGLs by measuring their viability after 48h exposure to a panel of 25 drugs spanning a broad chemical space, including both standard-of-care chemotherapy as well as targeted agents. The resulting drug sensitivity profiles highlighted shared responses but also tumor- and culture-specific differential responses. We will also discuss high-depth genomic sequencing comparison of the primary tumors and matched short- and long-term organoid cultures for a subset of cases, including VHL PPGL organoids. In summary, PPGL organoids are functionally active models that recapitulate aspects of neuroendocrine biology and can be used to investigate PPGL pathogenesis and drug responses.