Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Patient-derived organoids as a tool to assess drug response in pancreatic cancer

Synopsis:

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest of all types of cancer with a 5-year survival rate below 10%. The main reason for this poor prognosis is late diagnosis, with most patients (>70%) not eligible for surgery, which is currently the only potentially curative treatment. Most surgical patients are treated with systemic neoadjuvant or adjuvant cytotoxic chemotherapy. For those patients who are ineligible for surgical resection, palliative chemotherapy is usually performed, but the median overall survival for these patients is less than one year. The standard-of-care treatments are the combination chemotherapy regimens Gemcitabine/nab-Paclitaxel or FOLFIRINOX (5-Fluorouracil, Leucovorin, Irinotecan, Oxaliplatin), but there are no biomarkers for predicting which tumors will respond better to which regimen. Precision medicine therapies for patients with PDAC are just emerging. A PARP inhibitor (olaparib) has been approved for the maintenance treatment of adult patients with germline BRCA-mutated metastatic PDAC whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. However, few PDAC patients have BRCA mutations, and therefore are eligible for this new therapy. Thus, there is a need for alternative biomarkers to identify which patients with pancreatic cancer may benefit from precision medicine targeted approaches such as PARP inhibitors.

Despite significant advances in defining predictive biomarkers, it is not yet possible to predict if tumors will respond to therapy. In this prospective study, our goal is to establish proof-of-principle that patient-derived organoids - three-dimensional cell cultures derived from primary tumor cells - are a functional platform to evaluate tumor response. More specifically, we propose to generate PDAC organoids to assess drug response and compare their sensitivity profile with clinical response.

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