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Collection of lung adenocarcinoma Patient-Derived Xenograft (PDX) and PDX-derived organoids to evaluate precision therapeutic strategies

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Introduction:

Lung cancer is the most frequent cause of cancer-related deaths worldwide. The difficult detection of the disease in early stages and the modest efficacy of available therapies in advanced stages are responsible for the poor survival rates. Mutations in KRAS remain the most common driver alterations in non-small cell lung cancer (NSCLC). Whereas mutations in other oncogenes allow the use of specific inhibitors against this kinase, no specific therapies against KRAS are available for lung cancer patients. Therefore, there is a need to identify novel and effective tailored strategies to treat these patients. To accomplish this goal it is necessary to use in vitro and in vivo models that recapitulate the complexity of human cancers. Patient-derived xenografts (PDXs) and organoids have emerged as important platforms to elucidate new treatments and biomarkers in precision oncology. We aim to generate and characterize adenocarcinoma PDX and organoid collections to perform preclinical assays.

Method:

Resected primary tumors from lung adenocarcinoma patients were subcutaneous xenografted in athymic nude mice and expanded in successive groups of mice to get a perpetual live bank of each tumor. Every tumor was characterized histologically and molecularly. In order to generate PDX-derived organoids, the first step was the single-cell dissociation with collagenase and the suspension in Matrigel. For IC50 analysis, 10000 cells per well were plated in a 96 well plate. When 3D structures were formed, drugs were added in 100µL of media. Ten different doses were used for each drug, and three replicate wells were treated with each dose. 72 hours after the addition of the drug, cell viability was measured using a luminescence ATP-based assay.

Results:

We have established and characterized a PDX collection of 14 adenocarcinoma models derived from lung cancer patients, which retained the principal histologic and molecular characteristics of their donors, recapitulated their heterogeneity and represented the most relevant molecular alterations in lung adenocarcinoma. Using this PDX models we tried to establish a long-term PDX-derived collection, due to the low success in recovering from frozen stocks and expanding them in long-term passages, we decided to do short-term organoid cultures for testing different drugs. These short-term organoids cultures were developed from all these PDX models and were used to test different drugs in order to know their drug sensitivity and correlate with the results of the in vivo PDX treatments assays.

Conclusions:

We have generated a collection of 14 PDX models of lung adenocarcinoma characterized at the histological and molecular level, which represents the most frequent molecular subtypes of this type of cancer. Short-term organoid cultures can be established from PDX with 100% success rates. Propagation of early passage cultures produced a good tool for drug screening. These collections will be really useful to integrate drug screening with biomarker discovery and to evaluate precision therapeutic strategies.