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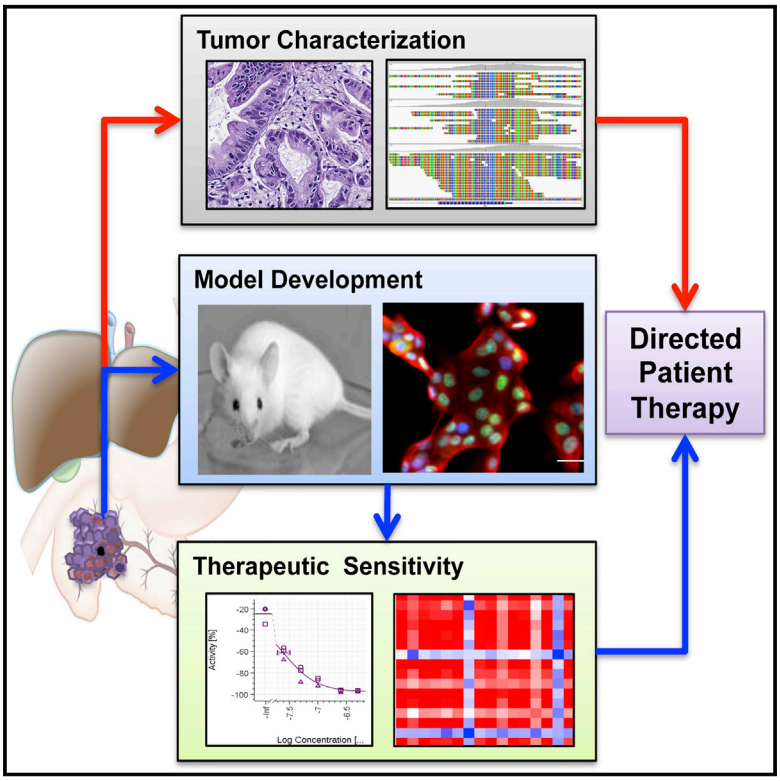
Cell Reports

Integrated Patient-Derived Models Delineate Individualized Therapeutic Vulnerabilities of Pancreatic Cancer

Graphical Abstract



Highlights

- Only a few genetic events in pancreatic cancer are currently sensitive to therapeutic targeting
- Patient-derived models can serve as the basis for empirically defined drug sensitivities
- There are few strong responses to single agents in patient-derived models
- Drug combination screens reveal diverse therapeutic sensitivities that are patient selective

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In Brief

Pancreatic cancer is therapy recalcitrant, and new approaches to therapeutic intervention are needed. Witkiewicz et al. used a large panel of patient-derived models to address the ability to use genetics or empirically determined sensitivities to guide treatment. These findings demonstrate a weakness of the current reliance on genetic analysis and suggest that using functional approaches with patient avatars could be particularly important for navigating the diverse therapeutic sensitivity of pancreatic cancer.

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Integrated Patient-Derived Models Delineate Individualized Therapeutic Vulnerabilities of Pancreatic Cancer

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SUMMARY

Pancreatic ductal adenocarcinoma (PDAC) harbors the worst prognosis of any common solid tumor, and multiple failed clinical trials indicate therapeutic recalcitrance. Here, we use exome sequencing of patient tumors and find multiple conserved genetic alterations. However, the majority of tumors exhibit no clearly defined therapeutic target. High-throughput drug screens using patient-derived cell lines found rare examples of sensitivity to monotherapy, with most models requiring combination therapy. Using PDX models, we confirmed the effectiveness and selectivity of the identified treatment responses. Out of more than 500 single and combination drug regimens tested, no single treatment was effective for the majority of PDAC tumors, and each case had unique sensitivity profiles that could not be predicted using genetic analyses. These data indicate a shortcoming of reliance on genetic analysis to predict efficacy of currently available agents against PDAC and suggest that sensitivity profiling of patient-derived models could inform personalized therapy design for PDAC.

INTRODUCTION

A precision approach to cancer medicine is transforming the way in which cancer is treated (Aronson and Rehm, 2015; Biankin et al., 2015). Conventionally, this approach relies on the use of markers to define a treatment strategy for a given disease. There are multiple successes attributed to precision medicine, from the current paradigm for breast cancer treatment stratification based on immunohistochemical markers (e.g., estrogen receptor [ER], progesterone receptor [PR], or human epidermal growth factor receptor 2 [HER2]) to the integrated genetic analysis of lung cancer that reveals multiple targets for therapeutic intervention (e.g., ALK [anaplastic lymphoma kinase] rearrangements or EGFR [epidermal growth factor receptor] mutations) (Deluche et al., 2015; Lindeman et al., 2013). Based on these and other successes, multiple clinical trials utilizing genetic information to guide patient treatment are open.

Pancreatic ductal adenocarcinoma (PDAC) harbors a particularly poor prognosis, and even after resection, long-term survival remains poor due to the frequent recurrence as metastatic disease (Almhanna and Philip, 2011; Kleger et al., 2014; Paulson et al., 2013; Yeo et al., 1995). Current systemic treatment of PDAC is dependent on chemotherapy, with minimal success of targeted approaches in the clinic. This therapeutic recalcitrance of PDAC is surprising, given substantial pre-clinical investigation and multiple provocative findings that would be expected to yield clinical benefit. This disconnect between preclinical testing and clinical outcomes suggests that more relevant models will be important for making significant inroads into the treatment of PDAC and that some form of patient stratification will be required to yield improved outcome. Notably, exceptional responses to therapy do occur in patients with PDAC (Garrido-Laguna et al., 2015), but these represent a very small segment of the treated population.

To date, pancreatic cancer has largely failed to benefit from the promise of precision therapy. In spite of substantial genetic analyses (Bailey et al., 2016; Collisson et al., 2011; Jones et al., 2008; Waddell et al., 2015; Witkiewicz et al., 2015), the path for the treatment of the majority of PDAC cases remains obscure.