VALIDATION OF A MOLECULAR SIGNATURE FOR THE PREDICTION OF THERAPEUTIC RESPONSE IN PANCREATIC CANCER

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Jo, Pablo López Ribelles , amb DNI 20908632E, sóc coneixedor de la guia de prevenció del plagi a la URV *Prevenció, detecció i tractament del plagi en la docència: guia per a estudiants* (aprovada el juliol 2017) (http://www.urv.cat/ca/vida-campus/serveis/crai/que-us-oferim/formacio-competencies-nuclears/plagi/) i afirmo que aquet TFG no constitueixen cap de les conductes considerades com a plagi per la URV.

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Abstract

Pancreatic cancer is a devastating disease that ranks as the seventh leading cause of cancer-related deaths worldwide. Unfortunately, treatment options for pancreatic cancer remain limited and surgical resection is only feasible for less than 20% of patients. The EGFR/RAS/MAPK signalling pathway, highly upregulated in PDAC tumours, has become the focus of extensive research due to its potential as a therapeutic target. Blasco et al. (2019) described that the combined genetic elimination of *Egfr* and *Raf1* induces regression in a significant fraction of *Kras/Trp53*-driven tumours in mice. In light of these findings, Liaki (2023) has established a molecular signature based on transcriptional differences in tumour cells to predict the response of mouse PDAC cell lines upon combined ablation of *Egfr* and *Raf1*. However, the power and accuracy of this molecular signature in classifying unknown PDAC cell lines as Responders or Non-Responders required validation.

Therefore, the objective of this project is to validate the established molecular signature and evaluate the potential of transcriptional analysis using RT real-time quantitative PCR to classify tumor cell lines as Responders or Non-Responders. Additionally, the study aims to delve into the resistance mechanisms associated with the ablation of *Egfr* and *Raf1*.

In order to achieve these goals, 15 mouse-derived PDAC cell lines were submitted to *Egfr*/*Raf1* silencing using short hairpin RNA technology to validate them experimentally as Responders and Non-Responders. These tumour cell lines underwent RNA sequencing to predict their response using the established molecular signature. The expression patterns of 5 of these lines were also studied by RT real-time qPCR. Finally, possible resistance mechanisms to *Egfr*/*Raf1* elimination were explored by targeting two additional genes in two Non-Responder cell lines.

The findings presented indicate that transcriptional profiling holds significant promise as a tool for predicting tumour response to targeted therapy. Moreover, the work carried out in this project has contributed to the validation of a gene panel capable of stratifying tumours based on their expression profiles. These advancements paved the way for the development of a valuable resource to aid in identifying patients who could potentially benefit from the targeted treatment involving *Egfr* and *Raf1*.

Keywords: Pancreatic ductal adenocarcinomas, molecular signature, *Egfr*, *Raf1*, targeted therapy