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PATIENT-DERIVED ORGANOIDS MAY PREDICT CLINICAL RESPONSE AND ENABLE PROSPECTIVE THERAPEUTIC SELECTION IN PANCREATIC CANCER

Pancreatic ductal adenocarcinoma (PDAC) is characterised by a very poor prognosis. Despite some minor therapeutic advances, median overall survival of patients with metastatic disease ranges from 6 to 11 months. Even for those who undergo potential curative surgery, expected median survival is below 27 months. Current treatment for both localised and metastatic disease is often based on unspecific characteristics, such as performance status and comorbidities. As many patients with PDAC are chemorefractory, there is an unmet clinical need to define responsiveness. Moreover, precision medicine approaches for pancreatic cancer are challenging.

In an article recently published in *Cancer Discovery* by a multi-institutional group of investigators, a successful methodology to develop pancreatic ductal carcinoma patient-derived organoids is described.[1] Seventy-five per cent of attempts to generate organoids did succeed wherever coming from both surgical resection specimens as well as fine needle biopsies. This is an important finding which enables prospective investigation on molecular classification and dynamic resistance to different anticancer agents in pancreatic cancer, where limitations such as amount and quality of available tissue and short survival are very relevant.

Using deep molecular characterisation of the patient-derived organoids' genome and transcriptome, the expected hallmarks of pancreatic cancer were identified and, interestingly, a very high concordance between the primary tumour and paired organoids was observed. The establishment of such stable models led to the possibility to perform sensitivity test to validate organoids' response to chemotherapy, comparing the results with the corresponding patient's clinical effect. Interestingly, it was possible to observe a huge concordance between responses to different agents of organoids and the one obtained by patients. Transcriptional signatures were also derived, mirroring patient outcomes in two separate clinical cohorts. One was made up of patients following adjuvant treatment with gemcitabine and the second was selected in the palliative setting after therapy with modified FOLFIRINOX or gemcitabine/nAb-paclitaxel. A great concordance was found in both cohorts, allowing the identification of patients who really have a long-term benefit from chemotherapy.

When organoids showed resistance to conventional chemotherapy, based on several mutations analysed, such as KRAS, PIK3CA, MAP2K, ERBB2 or even others, they were exposed in vitro to different tailored agents according to specific molecular features, exhibiting exceptional sensitivity to targeted agents, providing alternative treatment options for chemorefractory disease. This article shows that pancreatic cancer patient-derived organoids could modify the standard clinical approach. By this way, it will be possible to select those patients who will respond to chemotherapy. Moreover, through a comprehensive molecular analysis of organoids taken at baseline and beyond progression, a more personalised approach for the use of targeted agents can be pursued.

SHP2 INHIBITION MAKES POSSIBLE TO SUCCESSFULLY TARGET KRAS-MUTANT NON-SMALL CELL LUNG CANCER CELLS

In an interesting article published in *Nature Medicine*, Mainardi *et al* postulate SHP2 as having a key role to the issue of up-to-now unsuccessful KRAS targeting.[2] The SHP2 protein, encoded by PTPN11, was postulated to be a proto-oncogene. Ruess *et al* also published concurrently in *Nature Medicine* that biallelic deletion of *Ptpn11* in KRAS-mutated^{G12D} mice led to inhibition of pancreatic intraepithelial neoplasia development.[3] Comparable observations were made for KRAS non-small cell lung cancer (NSCLC) mice models.

Through a focused drug screen using PTPN11-knockout PDAC cells and NSCLC cells, Ruess and colleagues found PTPN11-knockout cells to be especially susceptible

to MEK inhibitors. MEK inhibitors have proven so far to be unsuccessful at targeting KRAS-mutant or KRAS-wild type NSCLC, in monotherapy or in combination with docetaxel.[4 5]

In their experimental model, Mainardi *et al* tried the AZD6244 inhibitor selumetinib against KRAS-mutant and wild type PDAC and NSCLC. They found that all six NSCLC KRAS-mutant cell lines underwent initial reduction in pERK following MEK inhibition, but that this was subsequently quickly restored coincidentally with an increase in SHP2 upstream activation. Similar findings were found in other cancer cell lines. This suggests an activation of an upstream feedback loops on MEK inhibition, which could account for restored downstream signalling. They tested tumour response to concomitant MEK and SHP2 inhibition with two different compounds. SHP2 inhibition by itself showed little effect, but the combination of both SHP2 and MEK inhibition showed a deeper antitumour effect. Western blot analysis also confirmed the reduction in pERK on combined inhibition. The effects of MEK inhibition seemed to be due to absence of phosphatase activity, as the restoration of SHP2 wild type, but not a phosphatase-deficient mutant conferred MEK inhibition resistance.

They neatly tested the effects of SHP2 and MEK inhibition in Rasless fibroblasts reconstituted with either KRAS wild type or KRAS mutant to study RAS GTP levels on MEK inhibition, while avoiding the confounding factor of KRAS-wild type protein in the cells. $KRAS^{G12V}$-reconstituted Rasless cells showed increased sensitivity to combined inhibition, suggesting that SHP2 inhibits KRAS activity.

These in vitro results were then confirmed in vivo in mouse models. They found that PTPN11 tumours failed to grow even in the absence of MEK inhibition, suggesting that SHP2 inhibition alone might be able to downregulate tumour growth in vivo. They postulate that SHP2 inhibition is dependent on growth factor availability with cells having the highest GTPase activity also being the most resistant to SHP2 inhibition. Combined SHP2 and MEK inhibition was effective in tumour regression even at the lowest selumetinib concentrations, while MEK inhibition by itself was not.

With up to 30% of NSCLC, 45% of colon cancer and 80% of pancreatic cancer being KRAS mutant, this is by far the most prevalent molecular alteration in patients with cancer, but it has thus far not found to be a targetable mutation despite much effort. The articles by Mainardi *et al* and Ruess *et al* in *Nature Medicine* are relevant in this respect as they shed light on the relevant KRAS resistance mechanisms and hopefully bring us nearer to effective KRAS targeting. Surely, this will be further pursued to elucidate the effectiveness of SHP2 inhibition in KRAS-mutant tumours, possibly in combination with MEK inhibition.

A 21-GENE EXPRESSION ASSAY TO GUIDE ADJUVANT TREATMENT IN BREAST CANCER

The 21-gene recurrence score assay is one of the available tests providing useful prognostic information in localised hormone receptor-positive breast cancer. The score ranges from 0 to 100 and when it is high, whatever over 26 or 31, it is predictive of a positive effect for the addition of chemotherapy. On the other hand, when the score is below 10, the expected recurrence rate at 10 years is by 2%, and therefore the addition of chemotherapy to adjuvant treatment could be considered as overtreatment. This gene expression assay was properly developed and validated in retrospective samples of women with node-negative oestrogen receptor-positive breast cancer accrued to phase III randomised clinical trials. Although strongly recommended by some experts, it was somehow uncertain if chemotherapy could be beneficial for patients with a mid-range recurrence score.

The Trial Assigning Individualized Options for Treatment was designed and conducted to determine the benefit of chemotherapy for patients with a mid-range recurrence score between 11 and 25. The analysis of this important study has been recently published in the *New England Journal of Medicine*.[6] More than 10 000 patients with breast cancer with hormone receptor-negative, HER2-negative without axillary nodal involvement were selected for the 21-gene expression assay and 69% of those eligible for this test, who got a mid-range recurrence score, were randomised to receive chemoendocrine therapy versus endocrine therapy alone.

This trial showed that endocrine therapy was not inferior to chemoendocrine treatment when invasive disease-free survival was analysed. At 9 years, both treatments showed similar rates of disease-free survival, freedom from metastatic disease recurrence or local disease recurrence as well as overall survival. The addition of chemotherapy did only show some benefit in women 50 years old or younger with a recurrence score of 16–25.

The clinical consequences of this trial are commented in an accompanying editorial.[7] In women older than 50 years with recurrence scores below 25, the addition of chemotherapy to endocrine therapy is unlikely to improve outcomes. In this way, we may avoid overtreatment with chemotherapy in a significant proportion of patients. However, chemotherapy provided a limited benefit to women who were 50 years of age or younger, when their recurrence scores between 16 and 25, and it should be considered to be added to endocrine treatment. Some other trials are ongoing to obtain similar information on the clinical usefulness of the 21-gene expression assay in a similar population of hormone receptor-positive breast cancer, but with axillary node involvement.[8]

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