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GASTROINTESTINAL CANCER

Organoids predict clinical responses

> the findings demonstrate the ability of PDOs to recapitulate clinical responses

Owing to their ability to recapitulate the histological and genetic characteristics of a primary tumour, patient-derived organoids (PDOs) have emerged as robust preclinical tumour models, but evidence of their ability to predict clinical outcomes is limited. Now, a new study published in *Science* reports that PDOs derived from patients with metastatic gastrointestinal cancer enrolled in phase I/II clinical trials can be used to predict clinical treatment responses.

"We decided to use organoids as they represent a rapid and cost-effective approach to test drug sensitivity in the lab, almost in real-time compared with patient treatment," explains lead investigator Nicola Valeri. A live biobank of PDOs was generated from biopsy samples from patients with chemorefractory metastatic colorectal cancer (mCRC; $n=16$), metastatic gastro-oesophageal cancer (mGOC; $n=4$) and metastatic cholangiocarcinoma ($n=1$), collected at baseline and after treatment (at progression).

The investigators first evaluated whether PDOs recapitulated the phenotypic and genotypic features of the parental tumours. Histological assessment revealed substantial morphological similarity between PDOs and parental biopsy samples, and further immunohistochemical staining demonstrated that oncogenic expression patterns were maintained *ex vivo*. Using next-generation sequencing, a 96% overlap in the mutational spectrum between PDOs and parental tumours was observed; similar results were reported for copy-number alterations and transcriptional profiles. Functional characterization of PDOs using 3D drug screening assays revealed several genotype–drug response correlations, illustrating their potential as drug-screening tools.

Valeri and colleagues next investigated the clinical predictive value of PDOs. In response to paclitaxel, a second-line treatment for metastatic gastric cancer, PDOs from a paclitaxel-sensitive mGOC tumour at baseline exhibited greater growth inhibition and apoptosis than PDOs from the same patient at progression, indicating the potential of PDOs for improving clinical treatment responses. Similar findings were reported for the first-line combination of 5-flurouracil and cisplatin in PDOs derived from chemosensitive and chemorefractory mGOC.

In chemorefractory mCRC, the response to FDA-approved therapies — including cetuximab, regorarenib and TAS-102 — was also assessed. Unsurprisingly, PDOs and matched biopsy samples harbouring $KRAS^{G12D}$ and $BRAF^{V600E}$ mutations did not respond to cetuximab. Interestingly, however, a PDO with genotypic characteristics suggestive of response (for example, *EGFR* amplification) did not respond to cetuximab, in line with the outcome of the patient, demonstrating predictive utility.

To model the anti-angiogenic effects of regorafenib, PDOs were orthotopically implanted in mouse livers. Regorafenib induced changes in the tumour microvasculature of PDO xenografts that were consistent with the clinical observations. Moreover, mice with PDO xenografts from a regorarenib-responsive tumour at baseline exhibited improved survival outcomes with regorarenib treatment compared with mice with PDO xenografts from the same tumour at progression, illustrating the ability of PDOs to capture tumour evolution and acquired resistance. Finally, using PDOs from a patient with mixed response to TAS-102, PDOs from TAS-102-responsive metastatic lesions were more sensitive to TAS-102 than those from rapidly progressing TAS-102-refractory lesions, demonstrating that PDOs can recapitulate intrapatient tumour heterogeneity.

Overall, the findings demonstrate the ability of PDOs to recapitulate clinical responses *ex vivo*, which could be exploited for personalized medicine applications. "We are setting up prospective trials where patients will be allocated to specific treatments based on *a priori* response observed in their organoids in the lab," concludes Valeri. "We are also working to incorporate inflammatory and immune cells in the *ex vivo* screening to account for the tumour microenvironment, and are trying to grow organoids from circulating tumour cells to capture cancer heterogeneity and avoid tissue biopsies".

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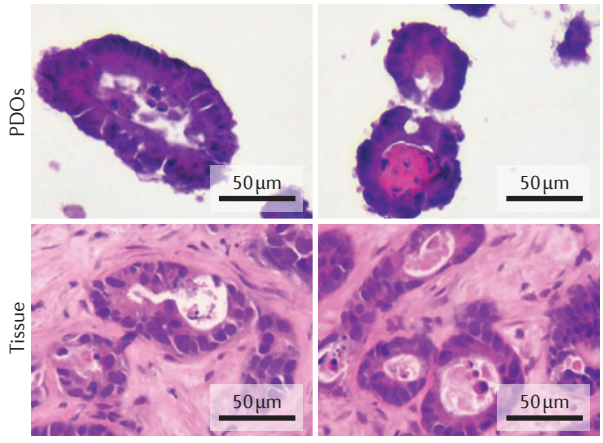

Histological assessment using haematoxylin and eosin staining reveals major morphological similarities between patient-derived organoids (PDOs) derived from patients with mCRC and their matched parental biopsy samples (tissue). Images courtesy of G. Vlachogiannis and N. Valeri.

ORIGINAL ARTICLE Vlachogiannis, G. *et al.* Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science* **359**, 920–926 (2018)