Title

An avatar for precision cancer therapy

Journal

Nature Biotechnology, 36(11)

ISSN

1087-0156

Authors

Kato, Shumei

Kurzrock, Razelle

Publication Date

2018-11-01

DOI

10.1038/nbt.4293

Peer reviewed

An avatar for precision cancer therapy

Screening patient-derived tumor cell cultures against a drug library as a promising adjunct to clinical decision-making.

Shumei Kato & Razelle Kurzrock

Center for Personalized Cancer Therapy and Division of Hematology and Oncology, UCSD Moores Cancer Center, La Jolla, CA 92093, USA. E-mail: rkurzrock@ucsd.edu

Precision oncology aims to match patients to therapies on the basis of the genomic alterations in their tumors. This approach of combining molecular diagnostics with therapeutics has not only transformed the standard-of-care management for certain malignancies[1–3], but is also integral to treatment selection in pan-cancer, precision medicine clinical trials[4,5]. In clinical practice, however, such factors as intra- and inter-tumor molecular heterogeneity and complexity have sometimes led to disappointingly low response rates, with responses that can be short lived. Therefore, the adoption of a more personalized N-of-one strategy that also examines the functional effects of genomic alterations may be necessary in order to enhance the efficacy of drug selection. In a recent issue of *Nature Genetics*, Lee *et al.*[6] demonstrate the feasibility of using drug screening of patient-derived cell cultures (PDCs) to guide treatment choice for individual patients. In their current publication, Lee *et al.*[6] demonstrated that PDCs faithfully represented the molecular landscapes of the original diverse cancer types. Furthermore, the authors exploit the PDC models to uncover new mechanisms of drug response and

resistance for multiple targeted agents and illustrate how PDC screens can provide evidence for repurposing agents against additional cancers.

Previous studies have looked at patient-derived organoids (PDOs; self-organized, three-dimensional tissue cultures)[7] or patient-derived xenografts (PDXs) (patient-derived tumor fragments engrafted into immunocompromised mice)[8] and have similarly found that these models often (but not always) recapitulate the molecular profiles of the parent tissue as well as patient responses. Lee *et al*.[6] derive a large number of tumor-sphere-forming PDCs (obtained directly from surgical specimens or malignant ascites) cultured in serum-free medium across 14 cancer types (from 462 patients). The PDCs were dissociated into single cells and seeded into 384-well plates (500 cells/well) and treated with a 60-drug library targeting major oncogenic signaling molecules (**Fig. 1**). After six days of incubation, cell viability was assessed using an adenosine triphosphate monitoring system based on firefly luciferase. These PDCs differ in some ways from others previously described, which were first grown on fibroblast monolayers and which utilized immunofluorescent indicators to verify cellular origin[9]. In comparing PDCs and PDOs, PDOs have the advantage of reflecting three-dimensional architecture and may include stromal cells, which may yield a more realistic recapitulation of cell-to-cell interactions than PDCs, since the latter are grown in monolayers; even so, PDOs have the disadvantage of being more complicated to develop and maintain than PDCs.

An important benefit of the PDC strategy is that they provide a rapid and facile readout of the ultimate functional effect on drug response that results from a complex array of genomic alterations in individual

patients. Further, PDCs not only deliver a faster timeline than PDX animal models, which require 6 to 7 weeks to become established versus 2 to 3 weeks for PDCs, but also are more amenable to large-scale, high-throughput drug screening. In the real-world oncology clinic, screening for drug sensitivity in a timely fashion is critical since patients may not be able to wait for several weeks before the treatment is selected. Further, tumors may evolve during longer time windows. There are also downsides to PDCs compared with PDX models in that PDCs do not include the tumor microenvironment, which can influence important factors such as angiogenesis. Finally, many current model systems including PDCs, PDOs and PDXs, cannot adequately recapitulate the immune system.

The 60 different targeted agents tested by Lee *et al.* [6] are commonly used in the clinical setting. They include inhibitors of receptor tyrosine kinases, such as platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) (PAM), as well as histone deacetylase inhibitors and more. All in all, the authors studied 27,720 drug–PDC combinations (60 drugs × 462 PDCs), which revealed diverse patterns of drug sensitivities. From this matrix, they first noted that certain cancer types are more vulnerable to certain classes of inhibitor. For example, PDCs from patients with colorectal cancer or glioblastoma were more resistant to PAM pathway inhibitors; in contrast, gastric cancer PDCs were more sensitive to these inhibitors. The authors further evaluated why gastric cancer PDCs were more sensitive to modulators of the PAM pathway using an

independent database (The Cancer Genome Atlas) and found that the PAM pathway is more active in gastric cancer.

Next, the investigators compared drug sensitivity and gene profiling results to determine whether specific gene markers in PDCs predict sensitivity versus resistance. This analysis led to robust clinically relevant discoveries. Among several important observations, the small-molecule drug ibrutinib, which is approved by the European Medicine Agency (Amsterdam) and the US Food and Drug Administration (FDA) for patients with chronic lymphocytic leukemia (CLL)—may also be efficacious for a subgroup of glioblastoma PDCs. Ibrutinib is an inhibitor of Bruton's tyrosine kinase, an important pathway for CLL. However, the investigators discovered that ibrutinib effectively targets epidermal growth factor receptor (EGFR), which was aberrant in glioblastoma PDCs, leading to high sensitivity of this lethal malignancy to ibrutinib. These findings are consistent with previous data suggesting that ibrutinib is capable of targeting EGFR (an FDA pharmacology review found a 50% inhibitory concentration (IC50) of 5.6 nM). This finding has major clinical implications for repurposing ibrutinib for patients with glioblastoma who harbor high levels of EGFR or *EGFR* mutations.

Several other important observations emerged from the authors' analyses. For instance, they established that *KRAS* mutations—which are present in over 20% of diverse cancers and are often considered not 'druggable'—had high sensitivity to targeted agents, including dasatinib (targeting SRC and BCR-ABL), BYL719 (a PI3K inhibitor) and trametinib (a MEK inhibitor). This observation is important, and consistent with a case report recently published showing that a patient with Rosai-Dorfman syndrome and a *KRAS* mutation had

a remarkable response to cobimetinib (a MEK inhibitor like trametinib)[10]. On the other hand, previous results from our group suggest that the use of PI3K inhibitors in patients with *RAS* alterations is associated with resistance [4,11]. Further investigation is required in this regard, especially as Lee *et al*.[6] demonstrate that certain drug combinations, such as MEK inhibitors combined with EGFR inhibitors, show improved efficacy in *KRAS*-mutated colorectal cancer.

Lastly, Lee et al.[6] evaluated whether the information gained from their *in vitro* PDC drug screening translated into improved patient outcomes. They show, in a sophisticated (albeit retrospective) manner, that a tumor was indeed more likely to be responsive to a targeted agent when the corresponding PDCs were sensitive to that agent. Multiple clinically applicable, approved anti-cancer agents including, but not limited to, afatinib (targeting EGFR), lapatinib (targeting Her2), sunitinib (targeting PDGFR-A) and everolimus (targeting mTOR) exhibited efficacy in patients with a variety of cancer types concordant with PDC predictions. Furthermore, if the PDC model demonstrated resistance, then resistance was more likely in the patient.

The above findings suggest that PDCs are capable of identifying potential targeted therapies for patients; indeed, the authors were able to correlate their findings with patient outcomes in the clinical setting in an elegant manner. They also show that this approach can uncover new mechanisms of drug response and resistance for a wide variety of targeted agents, depending on the presence of underlying genomic markers. The approach also provides evidence to guide the repurposing of drugs, such as ibrutinib, for aggressive cancers, such as glioblastomas.

Although innovative in multiple important ways, the study still requires validation in prospective clinical trials. Furthermore, next-generation studies may consider interrogating the PDC system with combinations of drugs, rather than monotherapies, as cancers with complex molecular portfolios are likely to require more than a single drug for optimized responses.

Overall, the work of Lee *et al.* [6] provides compelling evidence that PDCs may provide a useful model for individualized cancer therapy. To this end, the authors are moving forward with testing PDCs in the clinical trial setting (clinicaltrials.gov NCT#03170180), and we eagerly await the outcome of this prospective study.

Acknowledgments

This work was supported in part by the Joan and Irwin Jacobs Fund philanthropic fund; and by National Cancer Institute at the National Institutes of Health [grant P30 CA023100 (Razelle Kurzrock, rkurzrock@ucsd.edu)].

Competing interests

Razelle Kurzrock receives research funding from Genentech, Incyte, Merck, Serono, Pfizer, Sequenom, Foundation Medicine, Konica Minolta, Grifols, and Guardant, as well as consultant fees from Loxo, X Biotech, NeoMed, and Actuate Therapeutics, speaker fees from Roche, and an ownership interest in IDbyDNA and Curematch Inc.

1 O'Brien, S. G. *et al.* Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* **348**, 994-1004, doi:10.1056/NEJMoa022457 (2003).

2 Slamon, D. J. *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast

cancer that overexpresses HER2. *N Engl J Med* **344**, 783-792, doi:10.1056/NEJM200103153441101 (2001).

3 Soria, J. C. *et al.* Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* **378**, 113-125, doi:10.1056/NEJMoa1713137 (2018).

4 Tsimberidou, A. M. *et al.* Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): An MD Anderson Precision Medicine Study. *JCO Precis Oncol* **2017**, doi:10.1200/PO.17.00002 (2017).

5 Wheler, J. J. *et al.* Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. *Cancer Res* **76**, 3690-3701, doi:10.1158/0008-5472.CAN-15-3043 (2016).

6 Lee, J.-K. *et al.* Pharmacogenomic landscape of patient-derived tumor cells informs precision oncology therapy. *Nat Genet* (2018).

7 Vlachogiannis, G. *et al.* Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. *Science* **359**, 920-926, doi:10.1126/science.aao2774 (2018).

8 Gao, H. *et al.* High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nat Med* **21**, 1318-1325, doi:10.1038/nm.3954 (2015).

9 Kodack, D. P. *et al.* Primary Patient-Derived Cancer Cells and Their Potential for Personalized Cancer Patient Care. *Cell Rep* **21**, 3298-3309, doi:10.1016/j.celrep.2017.11.051 (2017).

10 Jacobsen, E., Shanmugam, V. & Jagannathan, J. Rosai-Dorfman Disease with Activating KRAS Mutation - Response to Cobimetinib. *N Engl J Med* **377**, 2398-2399, doi:10.1056/NEJMc1713676 (2017).

11 Janku, F. *et al.* Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. *Cell Rep* **6**, 377-387, doi:10.1016/j.celrep.2013.12.035 (2014).

Figure 1. PDCs as an avatar for individualized cancer therapy