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INVITED COMMENTARY

WILEY ORAL DISEASES

Patient-derived organoids: New co-clinical model to predict treatment response in cancer?

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One of the most relevant problems in clinical oncology is to know the response of each patient to the different treatments available, to be able to choose the best therapy, or combination of them, at the opportune moment once the cancer is diagnosed. Twenty years ago, trastuzumab was approved as therapy for breast cancer, an antibody directed specifically against the Her2 receptor that only a group of patients expressed in their tumors. This monoclonal humanized antibody is considered the first targeted therapy. Imatinib was approved only a few years later as a specific inhibitor of BCR-ABL fusion tyrosine kinase. These hallmarks laid the foundation for what we call now personalized medicine or precision medicine (Meisel, Venur, & Gnant, 2018; Prasad, Fojo, & Brada, 2016). Since then, great efforts have been made to identify specific molecular targets to develop high precision targeted drugs. The advent of new-generation sequencing (NGS), the "omics," and the management of big data has been fundamental elements in this task (Morash, Mitchell, Beltran, Elemento, & Pathak, 2018). However, preclinical models, both in vitro and in vivo, have not been able to reproduce the physio-pathological processes of patients, generating many expectations that have not been fulfilled. Thus, many promising results in these models have ended up failing in clinical studies. Even in clinical trials with promising results, a significant number of patients have shown no response to the treatment developed.

Main problems to be solved to recapitulate what happens in patients are the cellular heterogeneity of tumors and the selective pressure exerted by the different treatments on that heterogeneity. It is very difficult to mimic this condition in cell culture models, even when these are obtained from the same patient. The culture conditions may cause that specific clones are selected that are not necessarily representative of the original tumors, nor of the metastases. The development of three-dimensional (3D) cultures and the isolation of cancer stem cells and their growth in spheres have yielded some promising results in this regard (Ferreira, Gaspar, & Mano, 2018; Turetta et al., 2018). On the other hand, induced or spontaneous cancers in animal models are not representative of the analogous cancers in humans. Some years ago, orthotopic models were developed in immunocompromised mice for different types of human cancers (Lwin, Hoffman, & Bouvet, 2018). Although these models have been a significant contribution in the study of the cellular and molecular biology of the development and metastatic progression of these cancers, the results are insufficient for predicting the treatment response and evaluation of potential side effects. One of the main flaws of these orthotopic models is the absence of immune system in the animals. At present, the role of the immune system in the antitumor and tolerogenic cancer response is well known, so its influence is very difficult to disregard in any preclinical model. The return to syngeneic models (allograft) in humanized mice seems to be giving some results in immunotherapy, although its high cost may be a limitation (Ehx et al., 2018). These difficulties have significantly slowed down translational medicine, causing very few results generated in the laboratory (bench) to be satisfactorily applied in the clinic (bed). In this sense, reverse translational medicine, that is, the information collected and analyzed from the multiple clinical trials in different cancers, should give us a feedback on how to refocus our preclinical models (Brackman & Giacomini, 2018). A few years ago, the concept of co-clinical trials began to be developed to take advantage of the information from clinical and preclinical studies in parallel, improving the accuracy of new drugs aimed at specific targets and identifying the molecular pathways by which several patients are or become resistant to these therapies (Clohessy & Pandolfi, 2015).

Considering the enormous complexity of achieving advanced precision medicine and the rapid advancement of "omics" and bioinformatic and big data tools available, Vlachogiannis published, a few months ago, in *Science*, (Vlachogiannis et al., 2018) a study on patient-derived organoids (PDO) from gastrointestinal cancers. Organoids are culture systems that allow cells to interact with each other and with the environment in order to generate 3D structures (Xu et al., 2018). This type of cellular structure represents many advantages with respect to two-dimensional cell cultures, which

grow as flattened layers in culture plates. Lately, organoids have been used, as preclinical models, although their potential to predict clinical outcomes, particularly response to treatments and side effects, is not fully established. Vlachogiannis obtained PDO from patients with metastatic, heavily pretreated colorectal and gastroesophageal cancer enrolled in phase 1/2 clinical studies. In their study, the genotypic and phenotypic profiles of the PDO showed a great similarity with the tumors of the patients from which they were derived, which was verified both by immunohistochemistry and by amplification of oncogenic drivers. One of the outstanding aspects of this PDO characterization was the preserving of tumor heterogeneity, an essential issue in the representativeness of in vitro models. Surprisingly, PDO obtained at different stages of cancer progression and before and after treatments captured the spatiotemporal cell heterogeneity of the tumors, which was also observed when analyzing copy number alterations (CNAs) in PDO and corresponding biopsies. In addition, a high concordance was observed in mutations, CNAs, and transcriptomic profile after successive passages during months of culture. These results represent important characteristics of the PDO system to evaluate treatment responses. Another aspect that should be highlighted is the usefulness of PDO, obtained from metastatic patients, as tools for drug screening. Using a library of 55 drugs in clinical trials, a high correlation was found between the response to the drugs and alterations present in the PDO. For example, in the only ERBB2-amplified PDO, the highest response to lapatinib, a potent inhibitor of this receptor, was observed, inhibiting the entire signaling pathway and inducing apoptosis. However, in PDO without amplification of ERBB2, but with EGFR amplification (lapatinib also inhibits this receptor), only a slight inhibition of the signaling pathway was observed, but not apoptosis. These results were repeated with other drugs and their respective molecular targets. Undoubtedly, these findings are very promising in terms of the usefulness of PDO as effective predictors of drug response of the patients from whom they were derived. Congruence was also observed between the types of mutations found in the patients and PDO (i.e., PI3KCA) and the response to the respective drugs (i.e., GDC 0980).

From the point of view of PDO predictive capacity, the most important result was obtained by comparing the response to the different treatments of the patients enrolled in the clinical trials and their respective PDO. For example, the paclitaxel response of PDO from patients sensitive and resistant to this taxane was compared, finding a high congruence between patient and respective PDO. In addition, the sensitivity of PDO changes when they are obtained at different times of cancer progression. Surprisingly, a PDO from a patient initially sensitive to cetuximab (EGFR inhibitor) and that later progressed did not respond to the drug even presenting EGFR amplification, without mutations in KRAS and high levels of amphiregulin mRNA. Although these markers are predictive of response to cetuximab, the PDO showed no response as the patient from whom it was obtained, suggesting that PDO could be better drug-response predictors than genetic or molecular markers. This undoubtedly represents a very important advantage of PDO as a preclinical model. In addition to these advantages, PDO can also recapitulate tumor progression when grafted into orthotopic models, where the acquisition of resistance to the different treatments can be tested.

In the study by Vlachogiannis et al. (2018), the analyzed PDO showed 100% sensitivity, 93% specificity, 88% positive predictive value, and 100% negative predictive value in predicting response to target-directed therapy or chemotherapy. With these data, the use of these PDO can be postulated as a valuable complementary tool in therapeutic decision-making in precision medicine. Undoubtedly, more work is required to evaluate this model in other cancers and test its usefulness in combination therapies in different types of patients. Also, it would be interesting to analyze whether PDO are suitable to evaluate potential drugs' side effects integrating this information with pharmacogenetic studies of the patients.

Probably, technological advances in areas such as deep-learning, network analysis, systems oncology, and big data mining (Fucic, Aghajanyan, Culig, & Le Novere, 2018; Grapov, Fahrmann, Wanichthanarak, & Khoomrung, 2018; Ozturk, Dow, Carlin, Bejar, & Carter, 2018; Regge, Mazzetti, Giannini, Bracco, & Stasi, 2017) will help us to reorient the development and use of drugs in different types of cancer and in their different stages of progression, metastasis, and resistance. However, no doubt that models as PDO analyzed in the work of Vlachogiannis, integrated into co-clinical trials, can mean an important acceleration in precision medicine advances.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTION

Enrique Castellón wrote the commentary.

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