Improving precision stratification using patient-derived model systems

Due to the highly heterogeneous nature of cancer, it has long been recognized that a one-drug-for-all approach has a limited capacity to be effective. This, along with a deeper understanding of the complex and evolving nature of tumor biology, has led to the realization that personalized approaches are needed to improve treatment outcomes.

Precision oncology aims to match the right treatment to the right patient using specific features of the individual patient's tumor. Decisions are often based on sequencing tumor DNA and matching patients to targeted therapies according to the mutation profile of their cancer. While this approach has demonstrated some successes, results of the recent NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial, which is one of the largest precision oncology trials to date, revealed that response rates of those assigned to therapy were generally low (between 2% and 38%).[1,2]

To address this, there is growing advocacy for complementing genomics-based approaches with functional drug testing, which looks at the cellular response to drug exposure on a patient's live tissue to guide the right course of treatment. Patient-derived tumor models used for functional drug testing include freshly digested biopsies, 2D and 3D cell cultures, and patient-derived xenograft (PDX) models. Here, we provide examples of how the field has adopted these model systems to help guide precision stratification.

Direct profiling

Direct profiling involves perturbing freshly digested patient biopsies with different compounds in microtiter plates to determine drug sensitivity. The advantage of this approach is the ability to rapidly assess the tumor cells post-excision, meaning that tumor expression and immune populations are likely well preserved. A drawback of the model is that patient material is often limited and so only a few drug combinations can be tested.

Kornauth *et al*. recently demonstrated the application of this method to guide therapy decisions in patients with advanced aggressive hematologic cancers.[3] Using high-content imaging to determine single-cell phenotypes, the team first profiled the efficacy of 139 drugs on patient-derived samples. Cancer cell-containing tissue was acquired from patients by biopsy, bone marrow aspirate, or peripheral blood draws, plated on imaging microplates containing drugs, and stained with antibodies to distinguish between malignant or healthy cells. The cells were then subjected to high-content imaging and analysis to identify target cells and guide treatment decisions (Figure 1). Of the 56 patients treated based on this information, over half demonstrated a progression-free survival of at least 1.3 times the duration of their previous therapy.

Kropivsek *et al*. adapted this method to investigate drug and immunotherapy sensitivities of bone marrow samples from 70 patients with multiple myeloma.[4] The team used multiplexed immunofluorescence, high-content imaging, and deep-learning-based single-cell phenotyping to establish drug sensitivities. They then combined these findings with sample-matched genetics, proteotyping, and cytokine profiling to map the molecular regulatory network of drug sensitivity. The resulting data provided molecular insights into treatment response that the authors believe could be used to guide the selection of immunotherapies and combination therapies for precision medicine of multiple myeloma.

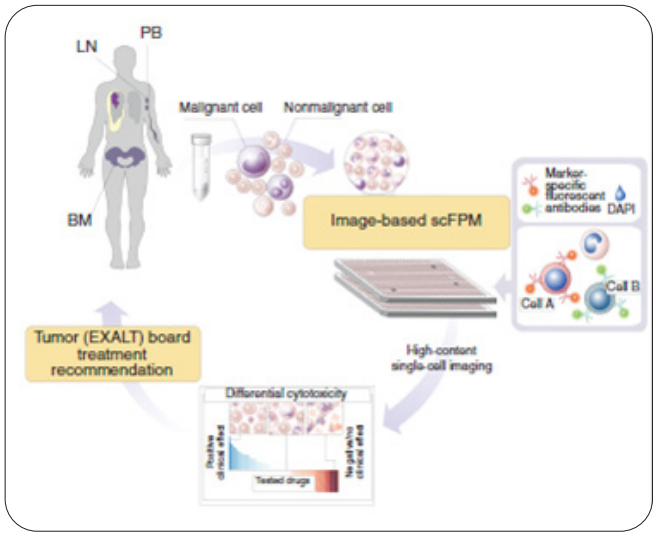

Figure 1: Viable cells from lymph node (LN), bone marrow (BM), or peripheral blood (PB) of patients with late-stage hematologic cancer were subjected to image-based single-cell functional precision medicine (scFPM). Target cells are identified by staining with fluorescent antibodies. Reports, automatically generated by the analysis pipeline, are discussed in a dedicated tumor board with patients treated accordingly. Image credit: Kournauth *et al.* 2021.[3]

Another group, led by Cecilia Bonolo de Campos, explored the applicability of drug sensitivity screening in multiple myeloma cell lines and primary samples.[5] A total of 76 drugs were evaluated and sensitivities were mined for associations with clinical phenotype, cytogenetics, genetic mutations, and transcriptional profiles. Their approach enabled the identification of six subpopulations of patients with distinct drug sensitivity patterns linked to genetic and mutational profiles, as well as clinical outcomes. For example, patient samples with biomarkers of poor prognosis had higher drug sensitivity to the recently FDA-approved drug Selinexor.

The findings of these studies illustrate the depth of information that can be gained from pairing direct profiling with molecular approaches and how this data could be used to guide individualized treatments for likely responders.

3D cell culture models

3D cell models are three-dimensional representations of cells, tissues, or organs that better represent the tumor microenvironment (cell morphology and viability, drug metabolism, and secretion) compared to traditional 2D culture models. Unlike direct profiling approaches, the expansion of patient material enables a greater number of drug combinations to be tested. Patient-derived organoids (PDOs) are a type of 3D cell culture model that can be established from primary patient tumors. Cells are either embedded in a matrix, cultured in suspension, or grown as a co-culture model. Researchers can expose the PDOs to various anti-cancer drugs and observe how the organoids respond to different treatments. This information can then be used to predict the likely effectiveness of specific drugs for that particular patient's cancer.

Georgios Vlachogiannis and colleagues demonstrated the ability of PDOs to accurately recapitulate metastatic gastrointestinal cancer patient's responses to treatment in the clinic.[6] The team generated a live organoid biobank from patients who had previously been enrolled in phase I or II clinical trials and compared organoid drug responses with how the patient responded. Critically, the organoids had similar molecular profiles to those of the patient tumor. The PDOs analyzed demonstrated 100% sensitivity, 93% specificity, 88% positive predictive value, and 100% negative predictive value in forecasting response to targeted agents or chemotherapy.

While PDOs offer numerous advantages for precision oncology, they also come with several limitations. Organoids can be difficult and time-consuming to establish and often require specialized equipment and technical expertise that is not always readily available. Variations in tissue quality, cell composition, and genetic mutations can also impact the reliability and reproducibility of PDOs. Nonetheless, organoids hold great potential to revolutionize cancer treatment by predicting the likely effect of specific drugs for an individual's cancer.

PDX models

PDX models are created by implanting a small piece of a patient's tumor tissue directly into immune-deficient mice. PDX models maintain many characteristics of the original patient's tumor, including histology and molecular profile, and can be used to assess treatment response in a context that closely resembles the human disease.

Letai *et al.* recently generated a collection of fibrolamellar carcinoma (FLC) PDXs and tested a library of over 5,000 drugs on cells dissociated from the PDX.[7] The efficacy

of the top hits was further validated in vivo in mice bearing PDX and then confirmed on tumor cells isolated directly from patient tissue after resection. The functional screens identified several novel compounds that were efficacious against cells dissociated from PDXs, in preclinical mouse models, and cells dissociated from patients. Interestingly, the researchers found that most of the drugs currently used in the clinic had minimal activity against FLC, demonstrating the value of such an approach to gain a personalized profile of therapeutic efficacy against solid FLC tumors.

Although PDX models are powerful tools for preclinical drug screening, they also have several limitations. Success rates for implantation are often low and the models typically take several months or more to grow. This can limit their ability to provide data in a clinically relevant timeframe. Mouse strains used for establishing PDXs also lack a functional adaptive immune system and therefore may not recapitulate the effect of therapeutics on anti-tumor immunity.

Summary

Precision oncology aims to transform how we treat cancer by matching the right treatment to the right patient at the right time. It acknowledges that each patient's cancer is different and therefore requires individualized treatment strategies. Patient-derived model systems are increasingly being used in functional drug testing to study the efficacy of a wide array of potential cancer treatments on live tissue derived from a patient. This information can then be used to predict likely responders and guide treatment regimens. The studies above illustrate the diverse application of functional approaches to the development of new cancer therapies and the advancement of precision oncology.

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