EUS-guided fine-needle technique-derived cancer organoids: A tailored “Shennong deity” for every patient with cancer

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During the last few decades, the treatment pattern for cancer has changed radically, and consequently, incurable diseases have been effectively controlled and even cured.[1,2] At present, in addition to preventive measures, there is a need to diagnose cancer as early as possible to treat it effectively. Moreover, we have to admit that, despite several advances, cancer remains a major health problem worldwide.[3] Patients exhibit varied responses to different antitumor drugs, resulting in drug resistance, which is a common phenomenon, thereby leading to reduced efficacy.[4] If we can accurately classify patients with cancer and identify the etiology and treatment targets based on clinical and genetic classification, we can provide personalized interventions and treatments as well as precise solutions, which will be of great benefit to patients with cancer.[5] In this milieu, precision medicine is highly relevant.

In general, precision medicine for cancer requires the following two key breakthroughs: one is screening of drug-sensitive targets by analyzing genetic abnormalities in numerous patients with cancer and the other is the validation of drug-sensitive targets through a large number of in vitro models that can maintain the characteristics of in vivo cancer cells.[6] The former has become a reality with the emergence of sequencing technology.[7] However, there is currently no reliable method to effectively detect drug sensitivity of cancer cells in vitro.

The commonly used in vitro cancer models include cancer cell lines and primary patient-derived tumor xenografts.[8] The complexity of tumors limits the application of the current cancer models in clinical settings. Moreover, while culturing cancer cell lines,
the heterogeneity and in vivo characteristics of cancer cells are often lost, resulting in the failure to reflect important characteristics of cancer cells. This affects the results of drug sensitivity tests, leading to limited clinical value and applications. Patient-derived tumor xenografts, to a certain extent, can simulate cancer conditions in vivo, but the disadvantages such as low transplantation success rate, long culture period, and high cost limit their application in clinical practice.

Recently developed three-dimensional (3D) culture techniques have led to the development of novel human cancer models that better reflect the physiological conditions in cancer. Small tissue fragments abstracted from larger organs are grown in a 3D matrix and then ultimately expanded into ex vivo organ-like structures, termed organoids. Since Sawyers and Chen first reported the successful culture of prostate cancer organoids from biopsied specimens and circulating tumor cells in 2014, research on organoids has opened a new era of personalized treatment for cancer. These personalized cancer organoids are essentially tiny tumor specimens that are grown in a culture dish, with characteristics of patients’ cancer cells and advantages of low cost and easy operation, which compensate for the defects of commonly used in vitro cancer models.

In 2015, van de Wetering et al. first constructed a living biobank with 22 colorectal cancer organoids and pioneered a new method for high-throughput drug screening using cancer organoids. It was confirmed by genomic DNA sequencing that the genetic mutations in these cancer organoids were highly similar to those in the corresponding tumor biopsy specimens. Moreover, the results were consistent with those of a previous large-scale colorectal cancer mutation analysis, proving that the cancer organoids inherit the genomic features of the source tumor. Huang et al. used pancreatic cancer organoids for testing two new drugs designed to treat pancreatic cancer. The results showed that the pancreatic cancer organoids were more sensitive to one of the drugs, confirming the feasibility of using cancer organoids as a platform to test personalized drugs. Vlachogiannis et al. used samples from 71 patients with metastatic gastrointestinal cancers, who participated in clinical trials, to establish a cancer organoid biobank. While predicting a patient’s response to different drugs through cancer organoids, the overall sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 93%, 88%, and 100%, respectively. This suggests that, if a cancer organoid responds to a drug, the drug has an 88% chance of being applicable to the patient.

Overall, cancer organoids maintain a high consistency with their source cancer tissues in terms of histology, molecular organization, and function from the beginning of organoid formation to the end of drug treatment, which may well reflect the characteristics of cancer in vivo. More importantly, they are of great value for clinical research in terms of testing and screening anticancer drugs. Furthermore, cancer organoids can help evaluate the sensitivity of anticancer drugs more quickly, reducing the waiting time from 6 to 8 months to a few weeks, thus gaining treatment time for cancer patients. Based on these advantages, cancer organoids offer a novel method for testing cancer drugs and cancer precision medicine, and they will play an increasingly important role in the treatment of cancer.

Until now, most cancer organoids have been successfully created by extracting tumor tissues from specimens during surgical resection. However, in most patients with cancer, the disease would have progressed to an advanced stage during diagnosis and is not suitable for surgery, which severely limits our ability to create cancer organoids.

EUS-FNA biopsy can help obtain an aspirate of tissue via a thin needle being inserted into the target structures under continuous real-time ultrasound guidance. The cells or tissues obtained from FNA can be smeared onto a slide and analyzed for abnormalities such as cancer. Using this technique, pancreatic cancer organoids have been successfully and rapidly created. In a prospective study of pancreatic ductal adenocarcinoma (PDCA), researchers evaluated the successful isolation rate of cancer organoids within 2 weeks after PDCA tissue obtained by EUS-fine-needle biopsy. Organoid isolation was confirmed based on organoid morphology and positive genotyping. Thirty-seven patients with 38 tumors were enrolled. Successful isolation of organoids was achieved for 33 (87%) of 38 tumors. The establishment of PDA organoid lines was achieved for 25 (66%) of 38 tumors.

Research on and treatment of cancer are of great significance to reliably produce organoids of patients with cancer. Therefore, the use of EUS-guided fine-needle technique for tissue collection during the initial diagnosis of cancer has the enormous
advantage of preparing cancer organoids, which can help select early and accurate drugs for almost all patients with cancer, and not just a few patients who can be surgically treated. Tissues obtained by EUS can be quickly processed in the laboratory for the preparation of organoids. As the EUS-guided fine-needle technique can reach the structure and tissues of the chest, abdomen, and pelvis,[16,18-20] this technique can potentially be used to prepare organoids from a variety of tumors for the treatment of patients with different types of cancer.

The EUS-guided fine-needle technique-derived cancer organoids highlight the future direction of clinical research in patients with cancer. Further studies on the consistency of genomic and transcriptional characteristics between EUS-guided fine-needle technique-derived and surgical-derived cancer organoids need to be refined.[17] Moreover, with the continuous development of organoid culture techniques, organoid cultures in the future will be more stable, efficient, and economical. This will not only revolutionize the treatment of cancer but also benefit patients with cancer.

In the era of precision medicine, EUS-guided fine-needle technique-derived cancer organoids will surely bring subversive changes to medicine. However, it is crucial to verify the effectiveness of this technique through successful matching between organoids obtained by this technique and by surgery. In addition, researchers should also pay attention to the ethical constraints associated with the development of cancer organoids.

Shennong, a mythological Chinese deity, is said to have tasted hundreds of herbs to test their medical value. We hope that the EUS-guided fine-needle technique-derived cancer organoids will become a tailored “Shennong deity” for every patient with cancer, enabling the use of different drugs for patients, delaying tumor progression, and consequently treating tumors.

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Conflicts of interest

There are no conflicts of interest.

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