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Original Article

Organoid biobanks as a new tool for pre-clinical validation of candidate drug efficacy and safety

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Abstract: The growing need for personalized medicine for cancer patients has enhanced and optimized the production of living tumor organoids that have become optimal preclinical models for the discovery and screening of anticancer drugs. The systematic collection and storage of tumor organoids through the establishment of dedicated biobanks will represent a fundamental tool for cancer research and clinical trials.

Keywords: Organoids, biobank, precision medicine

Introduction

Over the years, the stabilization of two-dimensional (2D) tumor cell models has allowed to conduct targeted functional studies that have elucidated the main mechanisms associated with tumor initiation and progression. For this reason, 2D cancer cell lines have become the most commonly used pre-clinical model system [1]. However, cultured cells have many limitations mainly because they do not mimic the natural tridimensional structures of tumor tissue and their initial establishment lead many molecular and phenotypic changes for the adaptation to cell culture conditions [2]. These alterations may influence several cell functions as cell growth, cell division, apoptosis, cell signaling and especially cell-cell and cell-microenvironment interactions.

For these reasons, three-dimensional (3D) organoid culture models have completely revolutionized in vitro studies for cancer research [3]. Organoid is a 3D *in vitro* cellular cluster deriving from stem cells or progenitor organs that spontaneously organize themselves in a similar way to their *in vivo* counterpart. There are several methods for obtaining organoids, including enzymatic dissociation and mechanical dissociation of tumor tissues to isolate spheroids with cellular heterogeneity, similar to the primary tumor. As a result, this model is capable of proliferation and can retain many of the features of the original tissues. In fact, tumor-derived organoids maintain the histopathology, gene expression, and genetic alterations of primary tumors. Their use has been abundantly validated for many human cancers, such as colon [4], prostate [5], pancreas [6], liver [7], gastric [8] and breast cancer [9]. Organoids have proven to be optimal preclinical models for pharmacodynamic profiling of human tumors [10]. This approach could replace the use of laboratory animals having proved its validity for quick selection and validation of drugs [11-13]. To measure the effects of anti-cancer drugs, the organoid surface, live cell count and volume-based growth rates are compared for different treatment conditions. Furthermore, the evaluation of 3D morphological changes, especially the sphericity and ellipticity parameters, are fundamental in the evaluation of the drug response. For several tumor types, such as Esophageal Cancer, Lung Cancer and pancreatic cancer, specific clinical trials to test sensitivity of the selected FDA-approved anti-cancer drugs have already been designed (https://clinicaltrials.gov/ct2/show/NCT03283527, https://clinicaltrials.gov/ct2/show/NCT03979170, https://clinicaltrials.gov/ct2/show/NCT03544255). These studies

Table 1. Organoid Biobanks from different cancers

Tumor Type	Biobank details	References
Colorectal cancer	Living biobank consisting of organoids derived from 20 patients.	[14]
Gastric cancer	Living biobank consisting of organoids derived from 34 patients.	[15]
	Living biobank consisting of organoids derived from 9 patients.	[16]
Breast cancer	Living biobank consisting of organoids derived from 100 patients.	[9]
	Living biobank consisting of organoids derived from 33 patients.	[17]
	Living biobank consisting of triple negative breast cancer organoids derived from 64 patients.	[18]
Bladder Cancer	Living biobank consisting of organoids derived from 16 patients.	[19]
	Living biobank consisting of organoids derived from 53 patients.	[20]
Prostate Cancer	Living biobank consisting of organoids derived from 20 patients.	[21]
Liver cancer	Living biobank consisting of organoids derived from 10 patients.	[22]
Pancreatic cancer	Living biobank consisting of organoids derived from 16 patients.	[23]
	Living biobank consisting of organoids derived from 30 patients.	[6]
	Living biobank consisting of pancreatic intraductal papillary mucinous neoplasms organoids derived from 8 patients.	[24]
	Living biobank consisting of pancreatic intraductal papillary mucinous neoplasms organoids derived from 15 patients.	[25]
Neuroendocrine tumors	Living biobank consisting of gastroenteropancreatic (GEP) neuroendocrine neoplasm (NEN) organoids derived from 39 patients.	[26]
Glioblastoma	Living biobank consisting of organoids derived from 53 patients.	[27]
	Living biobank consisting of organoids derived from 10 patients.	[28]
Lung Cancer	Living biobank consisting of non-small cells lung cancer organoids derived from 10 patients.	[29]
Kidney cancer	Living biobank consisting of kidney cancer organoids derived from 50 children.	[30]

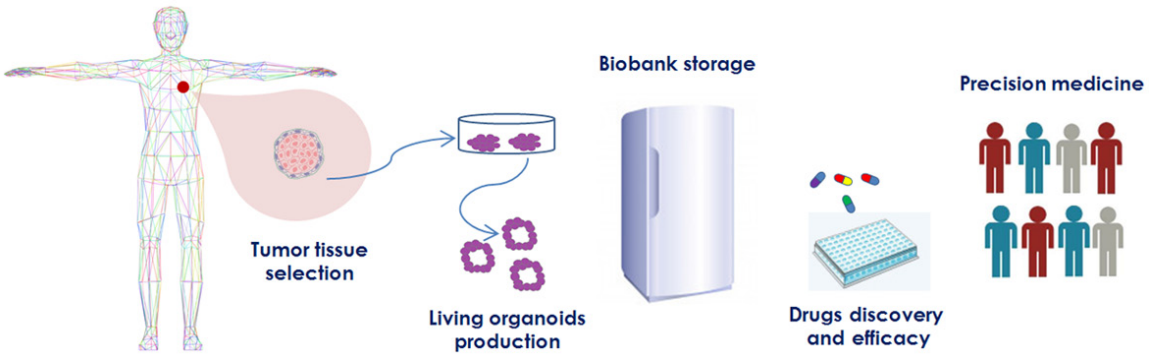

Figure 1. Schematic representation of the work flow from the production of living organoids to their conservation/biobanking and use in precision medicine.

are currently undergoing patient recruitment and the results are not yet known.

The enormous potential of organoids as pre-clinical models, and the growing need to create personalized medicine for cancer patients, has given rise to the need to establish collections of tumor living organoids matched with normal organoids from large numbers of individuals (**Figure 1**) [14]. The development of organoids biobanks has allowed the enhancement of studies associated with tumor drug screening and has allowed the identification of specific molecular signatures associated with altered drug response [6]. To date, organoid biobanks have been obtained from various tumor tissues, including colon [14], gastric [15, 16], breast [9, 17, 18], bladder [19, 20], prostate [21], liver [22], pancreas [6, 23-25], neuroendocrine [26], glioblastoma [27, 28], lung [29] and kidney cancer [30] (**Table 1**).

A series of benefits and limitations are associated with the use of organoids biobanks in clinical practice. Tumor organoids almost faithfully reflect the physiology of the tissue of origin, their production can occur in a short time and they can be used for genomic screening and large-scale drug screening. However, among the main limitations we must consider: i) the difficulty of reproducing the tumor microenvironment since the co-culture systems with other types of cells are not well defined; ii) the procedures for their creation are very different and linked to the tissue of origin, preventing an optimization of the methods; iii) they are quite expensive procedures that require specific expertise and rather long production times [31]. However, the main limitation is that, despite many organoid biobanks have been described over the years, standardized procedures for the conservation of living organoids have not yet been defined, unlike biological tissues and liquids biobanks. Likewise, ethical issues should also be better understood to be properly defined. In standardized biobanking procedures, the patient signs a specific informed consent for the safekeeping of biomaterials in a biobank certified for research purposes, properly formulated to protect privacy. The situation is much more complex for organoid biobanks for which the consent procedure should also include commercial interests, closely associated with the pharmaceutical industries for drug development and validation, and for the potential production of patentable products [32].

In conclusions, large-scale organoids biobanks will be a fundamental tool to screen the right drug to be used for specific patients and to support pre-clinical studies aimed at personalized medicine in a convenient or feasible way.

Disclosure of conflict of interest

None.

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