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Preview

The potential of patient-derived organoids in precision medicine of biliary tract cancer

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Chemotherapy resistance in biliary tract cancer (BTC) presents a major clinical hurdle. Ren et al.[1] developed and characterized an extensive collection of BTC patient-derived organoid (PDO) models, enabling advanced investigation of chemotherapy response prediction.

Biliary tract cancer (BTC) poses a distinctive challenge in oncology, primarily due to late-stage diagnosis and limited effective systemic treatment options.[2] Chemotherapy serves as the primary therapy for BTC patients, with variable responses and a dismal survival rate.[2] There is an urgent clinical need for predictive biomarkers of response to chemotherapy to advance precision medicine of BTC. Patient-derived organoids (PDOs) offer a reliable 3D *in vitro* model that closely mirrors the original tumor, facilitating cancer modeling and response prediction.[3] Compared with alternative patient-derived models, such as patient-derived xenografts (PDXs),[4] PDOs provide a cost-effective platform for high-throughput anti-cancer drug screenings. While numerous BTC PDO collections have been documented (Table 1), the utilization of large-scale BTC PDO collections for modeling and predicting chemotherapy responses remains limited.

Ren et al.[1] introduced a novel collection of 61 BTC PDO models, offering a promising avenue for BTC precision medicine (Figure 1). These BTC PDOs accurately recapitulate histopathologic and genomic features of their original tumors. They can be orthotopically or subcutaneously implanted into immunodeficient mice to generate PDO-derived xenografts (PDOXs) for *in vivo* research. Interestingly, clinical parameters of the original tumors, such as high tumor grade (stage IV), high tumor content, and intrahepatic localization, positively influence PDO generation. Transcriptional profiling also revealed that higher expression of "stemness and proliferation" genes and lower levels of "anti-proliferation" genes were associated with successfully established PDO models. Importantly, BTC PDOs displayed varying responses to distinct clinical chemotherapy agents, such as 5-fluorouracil (5-FU), SN-38 (an active metabolite of irinotecan), oxaliplatin, mitomycin C, and paclitaxel. These *in vitro* observations were subsequently confirmed in the PDOX models *in vivo*, and an impressive 92.3% agreement was found in BTC patients who exhibited actual clinical responses.

To explore the transcriptional characteristics associated with the response of BTC patients to chemotherapy drugs 5-FU (the active metabolite of capecitabine) and cisplatin, genome-wide transcriptomic studies were conducted on 19 BTC PDOs. The results revealed that genes involved in "tumor apoptosis" and "chemotherapy sensitivity" were upregulated in the 5-FU-sensitive BTC PDOs compared with the 5-FU-intermediate group response. Of note, among these genes, *TP73* has been reported to be involved as a pro-chemotherapy-sensitive factor in various tumor types.[9] Interestingly, gene set enrichment analysis (GSEA) also suggested Fanconi anemia and ataxia-telangiectasia mutated and Rad3-related (ATR) pathways as potential regulators of hypersensitivity to 5-FU. Furthermore, pathways involved in programmed cell death and *TP53* regulation were identified as enriched in the cisplatin-sensitive group, while genes related to drug resistance, such as *DDL4* and *DNAJC12*, were upregulated in the resistant group.

Finally, the authors have proposed a panel consisting of 13 genes for predicting response to 5-FU and a panel of 17 genes for predicting response to cisplatin. Employing support vector machine (SVM) and naive Bayes (NB) models, the authors have substantiated the exceptional discriminatory power of these gene panels in effectively distinguishing patients who exhibit a favorable response to chemotherapy from those who do not. These findings underscore the potential inherent in utilizing biomarker panels obtained from BTC PDOs to provide accurate predictions of patient responses to 5-FU and cisplatin.

This study by Ren et al.[1] presents a valuable platform of BTC PDOs that faithfully recapitulate the key characteristics of the original tumors and offer potential predictive biomarkers for patient responses to chemotherapy. However, several questions remain for future investigation. First, the challenge of long-term maintenance in BTC PDO is apparent, as 23% of the established models only supported short-term growth. A deeper exploration of the clinical, genomic, and transcriptional features contributing to sustained growth is warranted. Second, it is essential to validate the specificity and sensitivity of the proposed gene panels in larger and independent patient cohorts. This step is crucial for establishing the clinical significance and applicability of these panels in precision medicine for BTC. Finally, a growing body of evidence indicates that elements of the tumor microenvironment (TME), such as cancer-associated fibroblasts (CAFs) and immune cells, play a crucial role in determining drug response.[10] This holds significant relevance because the

Table 1. Comparisons of BTC PDO collections

	BTC PDO models		Tumor types				Characterizations			Drug screening	
Collections	Total	Success rate (%)	iCCA	eCCA	GB	Others	Histopathologic	Genomic	Transcriptomic	Drugs	Prediction model
Broutier et al.[5]	8	–	3	–	–	5	H&E, HepPar-1, EpCAM	WES	RNA-seq	29 drugs including cisplatin, 5-FU, doxorubicin, and gemcitabine	–
Lee et al.[6]	16	69.5	16	–	–	–	H&E, CK19, SOX9, PD-L1	WES	RNA-seq	gemcitabine and cisplatin	–
Saito et al.[7]	6	33.3	3	–	1	2	H&E, CK7, MUC1	WES	microarray	339 compounds, including antimicrotubule agents, mitomycin C, and aclarubicin	–
Kinoshita et al.[8]	60	88.2	5	49	1	5	H&E, CK7, HepPar-1	*TP53*, *KRAS*	–	–	–
Ren et al.[1]	61	74.4	44	13	4	–	H&E, CK19, CK7	WES	RNA-seq	gemcitabine, 5-FU, cisplatin, SN-38, oxaliplatin, mitomycin C, paclitaxel	yes, with the NB and SVM models

Abbreviations: BTC, biliary tract cancer; PDO, patient-derived organoid; iCCA, intrahepatic cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; GB, gallbladder cancer; H&E, hematoxylin and eosin staining; HepPar-1, hepatocyte paraffin-1; EpCAM, epithelial cell adhesion molecule; CK19, cytokeratin 19; SOX9, SRY-box transcription factor 9; PD-L1, programmed death-ligand 1; CK7, cytokeratin 7; MUC1, Mucin 1; *TP53*, tumor protein p53; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; WES, whole-exome sequencing; 5-FU, 5-Fluorouracil; NB, naive Bayes; SVM, support vector machine.

current standard of care for non-resectable BTC entails combining chemotherapy (i.e., cisplatin-gemcitabine) and the immune checkpoint inhibitor durvalumab, and the primary focus is to identify biomarkers for long-term treatment benefits.[2] However, the absence of TME components in current BTC PDO models hampers their integration into screening and biomarker

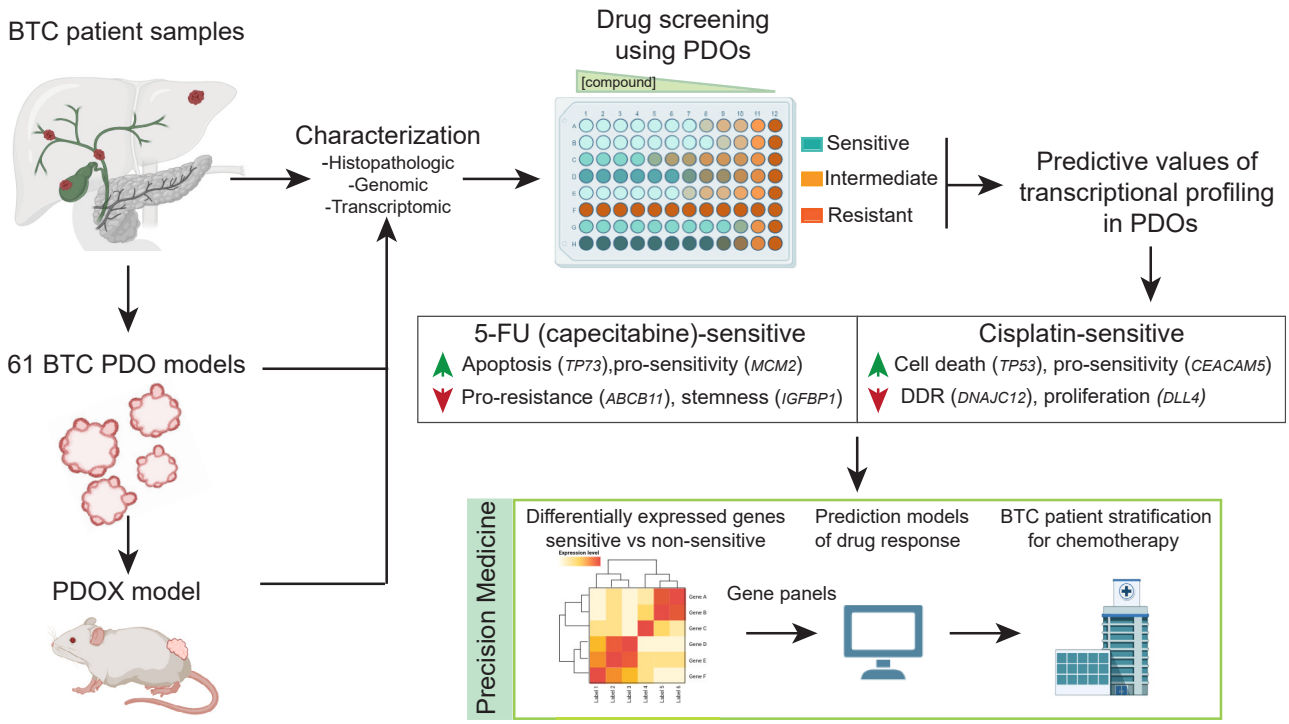

Figure 1. Development and application of BTC PDOs for chemotherapy drug-sensitivity screening and predictive biomarker discovery

discovery processes for TME-targeted treatments, emphasizing the need for further research in this area.

In summary, research utilizing patient-derived models for BTC holds promise for advancing precision medicine. These models have the potential to provide crucial insights into tumor characteristics and drug responses, offering hope to improve BTC patient outcomes.

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DECLARATION OF INTERESTS

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REFERENCES

1. Ren, X., Huang, M., Weng, W., Xie, Y., Wu, Y., Zhu, S., Zhang, Y., Li, D., Lai, J., Shen, S., et al. (2023). Personalized drug screening in patient-derived organoids of biliary tract cancer and its clinical application. Cell Rep. Med. *164*, S-1255.
2. Vogel, A., Bridgewater, J., Edeline, J., Kelley, R.K., Klümpen, H.J., Malka, D., Primrose, J.N., Rimassa, L., Stenzinger, A., Valle, J.W., et al. (2023). Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann. Oncol. *34*, 127–140. https://doi.org/10.1016/j.annonc.2022.10.506.
3. Veninga, V., and Voest, E.E. (2021). Tumor organoids: Opportunities and challenges to guide precision medicine. Cancer Cell *39*, 1190–1201. https://doi.org/10.1016/j.ccell.2021.07.020.
4. Serra-Camprubí, Q., Verdaguer, H., Oliveros, W., Lupión-Garcia, N., Llop-Guevara, A., Molina, C., Vila-Casadesús, M., Turpin, A., Neuzillet, C., Frigola, J., et al. (2023). Human Metastatic Cholangiocarcinoma Patient-Derived Xenografts and Tumoroids for Preclinical Drug Evaluation. Clin. Cancer Res. *29*, 432–445. https://doi.org/10.1158/1078-0432.CCR-22-2551.
5. Broutier, L., Mastrogiovanni, G., Verstegen, M.M., Francies, H.E., Gavarró, L.M., Bradshaw, C.R., Allen, G.E., Arnes-Benito, R., Sidorova, O., Gaspersz, M.P., et al. (2017). Human primary liver cancer-derived organoid cultures for disease modeling and drug screening. Nat. Med. *23*, 1424–1435. https://doi.org/10.1038/nm.4438.
6. Lee, H.S., Han, D.H., Cho, K., Park, S.B., Kim, C., Leem, G., Jung, D.E., Kwon, S.S., Kim, C.H., Jo, J.H., et al. (2023). Integrative analysis of multiple genomic data from intrahepatic cholangiocarcinoma organoids enables tumor subtyping. Nat. Commun. *14*, 237. https://doi.org/10.1038/s41467-023-35896-4.
7. Saito, Y., Muramatsu, T., Kanai, Y., Ojima, H., Sukeda, A., Hiraoka, N., Arai, E., Sugiyama, Y., Matsuzaki, J., Uchida, R., et al. (2019). Establishment of Patient-Derived Organoids and Drug Screening for Biliary Tract Carcinoma. Cell Rep. *27*, 1265–1276.e4. https://doi.org/10.1016/j.celrep.2019.03.088.
8. Kinoshita, K., Tsukamoto, Y., Hirashita, Y., Fuchino, T., Kurogi, S., Uchida, T., Nakada, C., Matsumoto, T., Okamoto, K., Motomura, M., et al. (2023). Efficient Establishment of Bile-Derived Organoids From Biliary Cancer Patients. Lab. Invest. *103*, 100105. https://doi.org/10.1016/j.labinv.2023.100105.
9. Müller, M., Schleithoff, E.S., Stremmel, W., Melino, G., Krammer, P.H., and Schilling, T. (2006). One, two, three–p53, p63, p73 and chemosensitivity. Drug Resist. Updat. *9*, 288–306. https://doi.org/10.1016/j.drup.2007.01.001.
10. Jin, M.Z., and Jin, W.L. (2020). The updated landscape of tumor microenvironment and drug repurposing. Signal Transduct. Target. Ther. *5*, 166. https://doi.org/10.1038/s41392-020-00280-x.