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The potential role of the 3D-bioprinting model in screening and developing drugs

Running title: 3D-bioprinting in drug development

Abstract
Recently, we have read with great interest the article by Alissar Monzer et al. this original article used different spatial configuration models of colorectal cancer (CRC) for validating the anti-tumor efficacy with Diiminoquinone (DQI). We feel obliged to provide new insight into the drug screening models by integrating and analyzing the original method and result. These comments may provide comprehensive insights into three-dimensional (3D) drug screening models and the difference between pathologic subtypes in CRC.

Keywords: Colorectal cancer; 3D-bioprinting; Mucinous adenocarcinoma; Drug screening models

Core Tip: Chemotherapy is the main treatment option for inoperable colorectal cancer. We recently read an article about the anti-cancer effects of DIQ. We feel obliged to express our opinion on this article on drug screening models and the difference between pathologic subtypes in CRC and hope it could deepen understanding for the reader.

TO THE EDITOR

We have read with great interest the article by Alissar Monzer et al [1]. The authors present a novel drug, Diiminoquinone (DIQ), with inhibitory effects for colorectal cancer (CRC) in different spatial configuration models. In vivo tests, Similar results have been obtained for drug effectiveness. In conclusion, the authors showed that DIQ may through suppresses Wnt/-catenin, AKT, and ERK pathways to the tumor and thereby inhibits tumor progression with significant potential to be translated into clinical practice.

The highlight of this study is that the authors used multiple 3D models to verify the effectiveness of DIQ. The 2D monolayer model has long been used in vitro cancer research for novel drug development and screening. However, 2D cancer cell models dramatically differ from cancer in vivo. Without spatial configurations, oncometabolite around the tumor microenvironment (TME) [2, 3], and intercellular signaling between the cancer cell and other cells, the result from the 2D module may be unable to draw correct conclusions, and this causes further challenges for clinic translation. In this research, sphere formation assays with tumor cell lines and derived organoids were established and used to prove the safety and efficacy of DIQ and to reflect more accurately drug sensitivity measurements result.

We found some details through in-depth analysis and hope to express some relevant views. 3D culture models should ideally recapitulate the native tumor microenvironment (TME). Despite sphere formation as a classic approach for 3D models, the limitation of this method is the lack of intercellular communication in multiple cell types. However, 3D-bioprinting provides several critical advantages over sphere formation assay in drug development or screening, such as using bio-ink to simulate the cytoskeleton or partial tumor tissue with multi-cell to a highly complex hierarchical 3D structure. These configurational were able to enhance intercellular communication and signaling factors transportation and provide a more accurate result for novel drug development [4,5]. Although the authors used organoid cultures to verify the drug's effectiveness at a later stage, the success rate of organ-like laboratory cultures is too low, which significantly limits the possibility of large-scale experimental validation. If 3D bioprinting is used, the required tissue size and culture conditions are lower than those of organoid cultures, which seems to provide more experimental samples for drug validation and enhance the data grade of this drug for clinical validation. Various 3D-bioprinting models were established, which aimed at disease modeling, novel drug development, and biological function evaluation [3, 6]. Therefore, based on the current research data, tumor modeling using 3D bioprinting technology after primary cell cultures seems to be more beneficial for chemotherapy drug sensitivity screening.

Another interesting finding was that the DIQ showed chemotherapy effectivity in mucinous adenocarcinoma (MC), a unique pathological subtype of CRC [7]. In a previous study, the chemosensitivity of mucinous adenocarcinoma was poor either irinotecan- or oxaliplatin-based therapeutic strategies than in non-mucinous tumors [8]. One mucinous adenocarcinoma patient tissue was successfully grown as an organoid model in the paper, which does not seem to provide sufficient evidence for the effectiveness of DIQ for colorectal mucinous adenocarcinoma. Nevertheless, the authors' experimental results provide a possible research direction for chemotherapy targeting pathological subtypes.

This original article uses multiple models of CRC to demonstrate DQI as a potential novel drug for chemotherapy. However, further research is needed to support the safety and efficacy of clinical translation.

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