A PDX-Derived Ex-Vivo Tumor Tissue Array Platform Utilizing Magnetic 3D Bioprinting for the Identification of Tumor-Specific Therapies

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Abstract

Great efforts have been undertaken in the field of cancer to develop clinically relevant pre-clinical models to permit the translation of research advances into medicines that can improve patient outcomes. The use of 2D monolayer and 3D monolayer tumor spheroid and cell culture systems has made this process remarkably costly and time-intensive. In contrast, the use of 3D magnetic and 3D magnetic 3D bioprinted tumor spheroid and cell culture systems has made this process remarkably cheaper and time-intensive. This review is a due in part to the discrepancies between the simplified in vitro cell culture model systems and the complex tumor microenvironment that is presented by these 3D cell culture models. The 3D cell culture models have been utilized to mimic different cancer types and subtypes, and to ultimately devise different therapeutic strategies that can be applied to different patients with various cancer types. This review will describe the recent advances in the generation of human tumor tissue platforms with magnetic 3D bioprinting, specifically in the generation of patient-derived xenografts (PDX) and cancer cell line printed (CCP) models. These models have the potential to become a viable option to study the effect of new drugs in a cost-effective and time-saving manner.

Methods and Results

Magnetic 3D Bioprinting

Figure 1: Schematic representation of a 3D bioprinting process. (A) Cell spheroidization of magnetic and non-magnetic cells in the same culture medium. (B) MagCellDrive device utilizing the magnetic field for spheroid formation. (C) Cell culture on 3D magnetic and non-magnetic scaffolds. (D) Immunohistochemistry analysis of the magnetic and non-magnetic cells on day 3.

Figure 2: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Prostate Cancer: Magnetic 3D Bioprinting

From PDX

Figure 3: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

From Bone Biopsy

Figure 4: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Figure 5: Prostate Therapeutic index is used to rank therapeutic index of different chemotherapeutic and targeted drug therapy. Therapeutic index has a very high predictive value in identifying tumor-specific therapies.

Magnetic 3D Bioprinting

Figure 6: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Inflammatory Breast Cancer (IBC) Comparison: PDX vs. Magnetic 3D Cell Culture

Figure 7: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Methods and Results

Magnetic Levitation

Figure 8: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Methods and Results

Tissue Morphology

Figure 9: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Genomic Comparison: PDX & Magnetic 3D Bioprinting

Figure 10: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Drug and Dose Response

Figure 11: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Drug Response

Figure 12: Schematic representation of the correlation of gene expression profiles between each set of tissue and magnetic bioprinting. (A) Total gene set, (B) specific gene set, (C) correlation analysis between each set of tissue and magnetic bioprinting.

Conclusions

- Utilizing the technology of magnetic 3D bioprinting, we developed a PDX spheroid tumor tissue platform for in vivo high throughput drug testing (HTDT) on human tumors from fresh tumor tissue biopsies, and a PDX mouse system generated from the same original tumor tissue and treated with the same panel of drugs. Utilizing an I

- The magnetic 3D bioprinted spheroids derived from human tumor tissue arrays have a high predictive value in identifying tumor-specific therapies.

- Incorporating the bioprinted ex-vivo tumor tissue array as an intermediary step within a PDX system will permit the identification of tumor-specific therapies in a time, cost and resource efficient manner.

- The bioprinted tumor tissue array is a preclinical platform that recapitulates the heterogeneity of the original tumor and serves as a clinically relevant screening platform.

- Platform compatible with high-throughput screening (HTS), 384-well plate format.

References

2. Niu B, M. et al. 3D printed and cultured from fresh tumor tissue, the cell culture plate should stay on the magnetic field is spherical, but more complex patterns can be generated. When (Fig. 1A) at the position and shape defined by applied magnetic field at the three-dimensional cell culture platform, the cell culture will be forced close contact between these cells and promote their survival. These cells release all its cellular content. Niu B, M. et al. This failure is also due to the similar techniques that have been used to force close contact between these cells and promote their survival.
3. The same drugs. Niu B, M. et al. We thank our patient advocates Terry Arnold and Sandra Bedrich Echardt, Naoto Ueno and Robert Amato for their support with prostate cancer research.
4. The methods described above, specifically collected from bone biopsies, cell culture on two different culture media have been utilized to mimic the primary tumor and different subtypes of cancer. A significant challenge associated with this use of PDX systems is that their generation requires immense resources, is costly and time consuming. In addition, they have limitations as platforms for high-throughput drug screens. Utilizing the technology of magnetic 3D bioprinting, we developed a PDX spheroid tumor tissue platform for in vivo high throughput drug testing (HTDT) on human tumors from fresh tumor tissue biopsies, and a PDX mouse system generated from the same original tumor tissue and treated with the same panel of drugs. Utilizing an I

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