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Biomanufacturing of an *In Vitro* Vascularized Platform for Pediatric Tumor Modeling

Liqun Ning, Jenny Shim, Kelly C. Goldsmith, Vahid Serpooshan

***Abstract*— Neuroblastoma (NB) is the most common extracranial solid tumor of childhood and have been extensively characterized at the genetic/ epigenetic levels, yet the role of the tumor microenvironment (TME) remains elusive. Therefore, biomimetic experimental models to elucidate the TME cellular and molecular mechanisms contributing to NB progression would prove useful in furthering our understanding of NB pathogenesis. This study utilizes advanced biomanufacturing and cancer spheroid technologies to develop a vascularized model that closely recapitulate the complex TME. Results demonstrate the robust potential of the developed model to study NB growth, aggression, and interactions with vasculature. The engineered platform can therefore be used for high-fidelity analysis of how the TME contributes to NB growth, metastasis, and response to diverse therapies.**

***Clinical Relevance*— The developed *in vitro* platform can be used to assess the mechanisms and efficacy of various clinical therapies to treat cancer within an environment that more faithfully recapitulates the human condition.**

I. INTRODUCTION

Current models to study neuroblastoma (NB) provide either overly simplistic view of tumor biology (2D models), or inconsistent operations and results (animal models), therefore motivating the development of new methods that can reliably recapitulate the complex microenvironment of pediatric tumors. Here, we designed and manufactured a vascularized NB tumor model using embedded 3D bioprinting technique. By loading an NB spheroid and human endothelial cells (ECs) into the model, we explored the function of NB cells in terms of their viability, protein expressions, and the NB-EC interactions. Results demonstrate the great potential of developed model as a research enabling platform to investigate the pathological mechanisms of NB tumor.

II. METHODS

Embedded 3D bioprinting was conducted following our previously developed method [1]. Gelatin methacrylate (gelMA) was prepared at 10% w/v and used as bioink. A 0.4% w/v Carbopol solution was used as embedding bath. The printing parameters were optimized to preserve the structural accuracy and reproducibility. Following UV polymerization, bioprinted constructs were transferred to a culture plate for NB spheroid and EC loading. The growth of the NB spheroids, including their size, cell viability, and protein expressions was analyzed over a 2-week *in vitro* culture.

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Vahid Serpooshan is with the Emory University and Georgia Institute of Technology, USA. E-mail: vahid.serpooshan@bme.gatech.edu.

III. RESULTS

An NB model with high (>90%) structural fidelity was created following the CAD design (Fig. 1A-B). The NB spheroid, loaded in the center of the construct, showed significant growth over the 2-week culture (Fig. 1C) with a high cell viability (over 70%, Fig. 1D and 1G). Confocal imaging revealed the active interactions between NB and ECs, where NB and ECs infiltrated into each other (Fig. 1E-F). With extended culture, the migration distance of NB cells became longer, and the infiltration of ECs towards the central hypoxic zone of the NB spheroid was significantly increased (Fig. 1H-I).

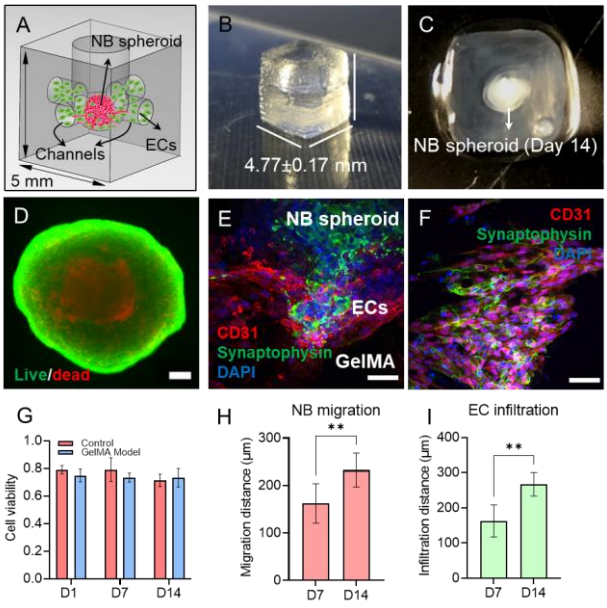

Figure 1. 3D bioprinted NB model and its capacity to support NB growth. A: Schematic design. B: Printed model. C: NB spheroid culture in the model. D: Live/dead assay. E-F: Interaction between NB and ECs. G: NB cell viability. H: NB cell migration. I: EC infiltration. Scale bar: 200 μm.

IV. DISCUSSION & CONCLUSION

Advanced 3D bioprinting is capable of creating *in vitro* NB models with high architectural accuracy, which could provide a robust and biomimetic microenvironment for NB tumor modeling. This model could serve as a platform for studying the pathological mechanisms of NB and the development of new therapies to treat a wide variety of cancers.

REFERENCES

[1] L. Ning, R. Mehta, C. Cao, A. Theus, M. Tomov, N. Zhu, E. R. Weeks, H. Bauser-Heaton, and V. Serpooshan, "Embedded 3D Bioprinting of Gelatin Methacryloyl-Based Constructs with Highly Tunable Structural Fidelity," *ACS Applied Materials & Interfaces,* vol. 12, no. 40, pp. 44563-44577, 2020.