Development of a Highly Porous Bioink to Enhance Microvessel Network Formation in Vascularized Tumor Microenvironment Models

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Introduction

In the tumor microenvironment (TME), tumor vascularization is crucial for tumor growth and metastasis. As a tumor grows, it must recruit blood vessels to deliver oxygen and nutrients and remove waste because cells cannot survive if they are more than 200 μm away from a blood vessel. The vessel network around the tumor is very complex and consists of numerous microvessels, making it difficult to mimic the tumor microvessel network in TME model fabrication. To overcome this challenge, we developed a porous collagen bioink to mimick the complicated microvessel structure around the tumor. The porous structure of this bioink provides an optimal environment that supports the infiltration of microvessels, promoting cellular interactions and facilitating nutrient and oxygen exchange. To further enhance vascularization while maintaining structural stability, we developed a porous bioink by incorporating air into a collagen–fibrin composite. The incorporation of air generated a highly porous architecture without altering the intrinsic biochemical properties of the matrix components. This collagen/fibrin porous bioink was compatible with bioprinting and exhibited stable, reproducible printability. Also, this is expected to serve as a promising platform for the fabrication of vascularized tumor microenvironment (TME) models in future studies.

Materials and Methods

▪ Materials

Collagen (MSBio, South Korea), Fibrinogen (Sigma Aldrich, USA), Thrombin (Sigma Aldrich, USA), Genipin(TCI, Japan), EA.hy926 (ATCC, USA), Colo320DM (Korean Cell Line Bank, South Korea), Dulbecco's Modified Eagle's Medium High Glucose (Welgene, Korea), Fetal bovine serum (Sigma Aldrich, USA), Penicillin/Streptomycin (Capricorn Scientific, Germany)

▪ Methods

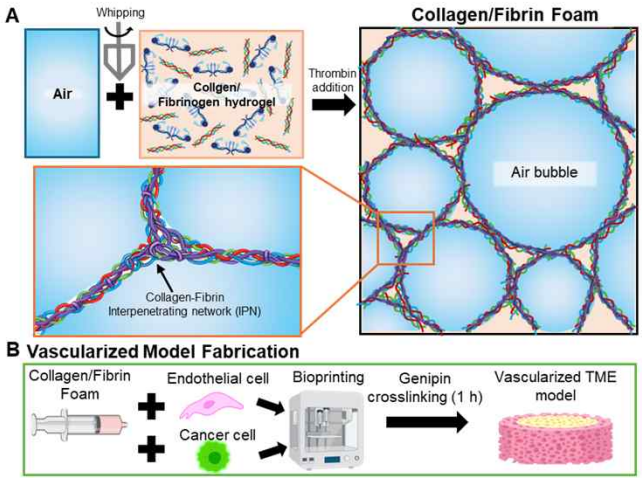


Figure 1. Schematic of (A) air incorporation into a collagen/fibrinogen hydrogel and collagen–fibrin network formation, and (B) the bioprinting process used to fabricate a vascularized model.

Results and Discussion

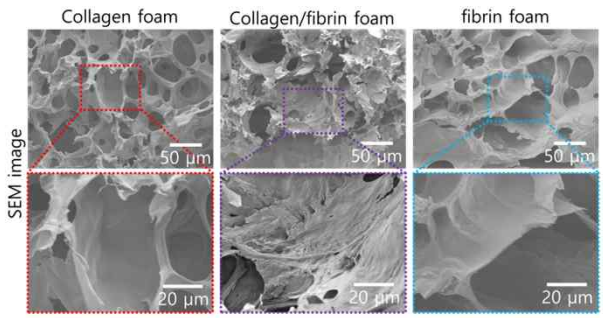


Figure 2. SEM images of collagen foam, collagen/fibrin foam, and fibrin foam. The concentration ratio of collagen/fibrin foam is 1:1.

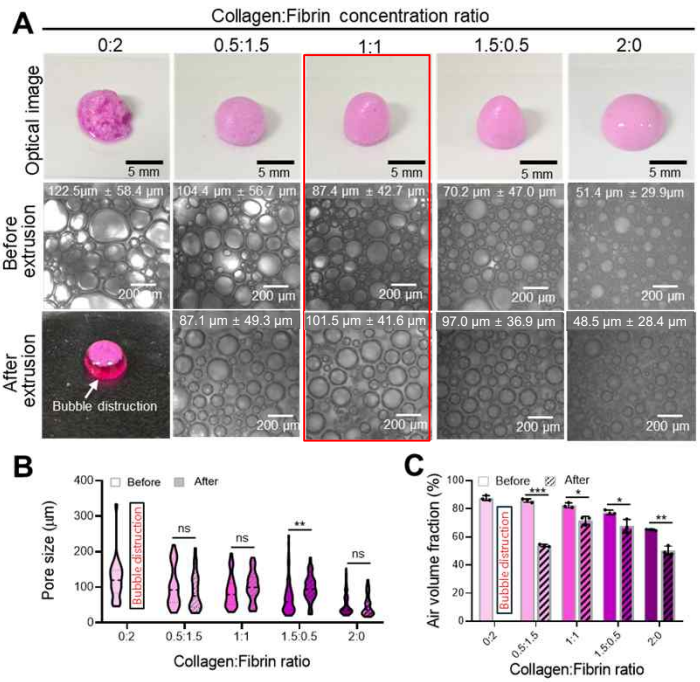


Figure. 3. (A) Optical images of the foam hydrogel and microscopic images of the foam hydrogel before and after nozzle extrusion (nozzle diameter: 330 μm) at different collagen/fibrinogen concentration ratios. (B) Pore size distribution and (C) air volume fraction of the foam hydrogel before and after nozzle extrusion.

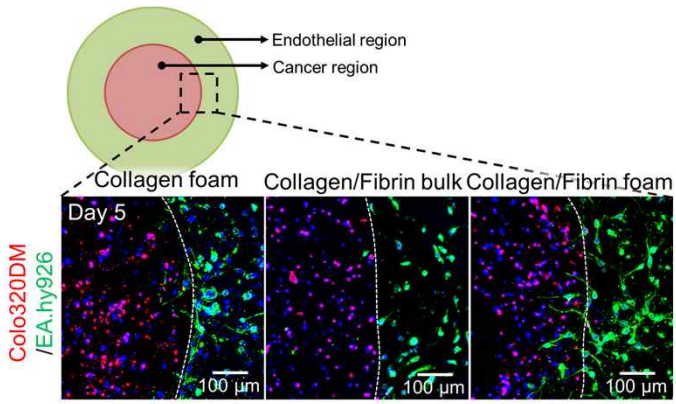


Figure. 4. Cell-tracker images of TME models fabricated using collagen foam, collagen/fibrin bulk, and collagen/fibrin foam bioinks at day 5.

Conclusion

In conclusion, our findings demonstrate that the formation of a collagen–fibrin interpenetrating network (IPN) enables the fabrication of a structurally stable porous foam bioink with high air volume fraction. The resulting collagen/fibrin foam maintained its porous architecture even after nozzle extrusion during the bioprinting process. Compared to collagen-only systems and bulk systems, the collagen/fibrin foam exhibited significantly enhanced vessel infiltration into cancer region. Collectively, these results suggest that the collagen/fibrin foam bioink provides a promising platform for the development of vascularized tumor microenvironment (TME) models.

Acknowledgement

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