Tissue Engineering

Tissue Engineering - Poster Session A

Poster BB6 - Bespoke Bioprinting of Stem Cell-derived Pancreatic Islets and Vasculatures within the Engineered Peri-Islet Niche

Thursday, October 24, 2024 10:00 AM – 11:00 AM EST

Location: Exhibit Hall E, F & G

Presenting Author(s)

MK

Myungji Kim, PhD

Ph.D student
POSTECH
Pohang-si, United States

Co-Author(s)

Dong Gyu Hwang (he/him/his)

Post-doc researcher
Pohang University of Science and Technology (POSTECH)
Pohang, Kyongsang-bukto, Republic of Korea

Primary Investigator(s)

Jinah jang, PhD (she/her/hers)

Associate Professor
Pohang University of Science and Technology (POSTECH)
Pohang-si, Kyongsang-bukto, Republic of Korea

Introduction: Pancreatic islets are dense cellular aggregates containing various types of hormone-producing cells crucial for regulating blood glucose levels. Interactions among these cells significantly influence the glucoregulatory functions of islets, as well as the surrounding niche and pancreatic tissue-specific geometry. However, stem cell (SC)-derived islets generated in vitro often lack the 3D extracellular microenvironments present in native islets, leading to structural instability and impaired coordination of islet-extracellular matrix (ECM) signaling, which is critical for functional maturation. Additionally, the absence of peri-islet vasculature further contributes to the immaturity of SC-derived islets, reducing their ability to detect glucose fluctuations and release insulin promptly. To overcome these challenges, we propose bioengineering in vivo-like islet niches by (1) reproducing the islet-specific microenvironment through optimizing the combination of pancreatic tissue-specific ECM and basement membrane (BM) proteins and (2) utilizing bioprinting-based geometrical guidance to recreate the spatial pattern of islet peripheries, facilitating coordinated interactions between islets and vasculatures. The bioprinted bespoke islet-specific niches enabled the structural and functional resemblance of SC-derived islets to native pancreatic islets. Moreover, we investigated how bioprinted human

islet-like cellular aggregates and vasculatures (HICA-V) respond in a physiologically mimicking manner to hyperglycemic conditions, with the goal of assessing its potential applicability as an anti-diabetic drug testing platform targeting islet niches representing both dysfunctional and healthy states. Our engineering perspectives, focusing on meticulously optimizing niche properties to reproduce tissue-specific organization, hold pivotal potential for advancing research in islet development, maturation, and diabetic disease modeling in a clinically applicable manner.

Materials and

Methods: Development and characterization of peri-islet niche-like (PINE) bioink
To identify the major ECM protein composition of collagen type I (Col) and pancreatic tissue-derived decellularized ECM (pdECM) bioinks, proteomic analysis was conducted using Matrisome DB and PANTHER DB. After investigating the pancreatic tissue-specific composition, PINE bioink was fabricated by supplementing BM proteins at a concentration of 100 μg/mL to the pdECM bioink. To characterize niche effects on functional maturation, differentiated islet cells derived from the H1 embryonic SC line were encapsulated in Col, pdECM, and PINE bioinks, and their immunofluorescence intensity profiles of hormones, β cell-related gene expression levels, and glucose responsiveness were evaluated. Additionally, the rheological properties of each bioink were assessed to demonstrate shear-thinning behavior and a self-healing process for the stable localization of the printed cells.
Fabrication and functional validation of HICA-V
A micro extrusion-based 3D bioprinting system was used to fabricate HICA-V. For in-bath bioprinting, PINE bioink was filled within the polymeric frame as a bath. Subsequently, EC-laden PINE bioink was extruded in a linear pattern to print vasculature within the bath. For HICA, SC-derived islet cells and EC-laden PINE bioink were printed in an aggregate shape. Following this, the bioprinted HICA-V underwent incubation at 37 °C for 1 hour and was then supplied with CMRL: EGM2 medium. Physio-mimetic responses of HICA-V were examined under hyperglycemic conditions induced by 30 mM of glucose. In drug treatment groups, 0.8 μM of empagliflozin and 20 μM of metformin were utilized for the drug response investigation.

Results, Conclusions, and Discussions: In this study, we proposed the creation of bespoke bioprinting-based islet-specific niches to promote the glucoregulatory functions of SC-derived islets by replicating the functional coordination observed among islets, ECM, and vasculature in vivo. Our approach involves recreating the specific environmental niche of pancreatic islets by refining the combination of pdECM and BM proteins, which are crucial for the metabolic functions of insulin-secreting β cells. Additionally, we utilized bioprinting-based geometrical guidance to recapitulate the spatial arrangement of islet peripheries, improving synchronized interactions between printed islets and the vasculature. The bioprinted HICA-V using the PINE bioink successfully achieved critical features resembling native pancreatic islets, such as highly aggregated islet morphogenesis and a tight connection with the vascular networks, indicated by abundant expression of adhesive proteins (e.g., Cadherins and EphA/ephrin A) that induce timely insulin secretion with enriched signaling molecules. We also observed stable glucose responsiveness, high expression levels of metabolic markers, and physiologically relevant responses ranging from healthy to diabetic states, including upregulation of inflammation and vasoconstrictive proteins under the hyperglycemic conditions and restoration of insulin secretory

functions after combinatorial anti-diabetic drug treatment. Overall, the HICA-V within the engineered peri-islet niche demonstrated optimal customization, incorporating both biochemical and biophysical cues to promote functional maturation and overcome the limitations associated with the immaturity of SC-derived islets. These synergistic biomanufacturing approaches led to significant improvements in functional output under both healthy and diabetic disease-like conditions, closely mimicking native islet physiology. This innovative perspective opens promising avenues for mechanistic studies investigating how environmental factors influence islet development, maturation, and the modeling of diabetic diseases, thereby enhancing the potential for translating diabetic therapeutics into clinical applications. Further, our insights into developing bespoke niches suggest an adaptable concept for functional transplants to treat diabetes, applying a biochemically defined matrix and hierarchically arranged cells in a peri-islet-specific manner.

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