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DEVELOPMENT OF A 3D-BIOPRINTED PULMONARY ARTERIAL SMOOTH MUSCLE TISSUE MODEL TO STUDY PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

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Background:
One in every 500 live births is affected by a life-threatening condition called persistent pulmonary hypertension of the newborn (PPHN). Increased vascular stiffness contributes to pulmonary arterial smooth muscle (ASM) dysfunction in PPHN, however studying this structural defect using traditional experimental methods poses challenges.

Objective:
Using 3D-bioprinting technology, we aim to fabricate pulmonary ASM tissue constructs with modifiable stiffnesses to mimic diseased pulmonary arteries. We hypothesize that our model will replicate PPHN, enabling us to demonstrate that increased stiffness contributes to pulmonary ASM dysfunction.

Methods:
Various bioinks with modifiable stiffnesses were composed of a combination of 0.25% to 0.5% w/v alginate, 1 mg/mL collagen and 5 mg/mL fibrinogen. Pulmonary and coronary ASM cells ($2.5x10^7$ cells/mL) were encapsulated in bioinks and bioprinted into 8mm rings with or without a load-bearing framework. Constructs of various stiffnesses were compared to assess integrity and functionality. Tissue compaction was assessed by reduction of lumen area. Cell organization was determined using filamentous actin (f-actin) staining.

Results:
Across all stiffnesses and cell types, f-actin staining demonstrated that cells within the constructs started elongating within 24 hours of printing, indicating that the cells are interacting with integrin binding sites in alginate, collagen, fibrin and on other cells. Pulmonary ASM constructs with no framework (0.5% alginate) had a 70.57% lumen reduction within 24 hours of printing rendering it non-functional. In contrast, the load bearing framework prevented the constructs from collapsing with only 3.69% lumen reduction. This design promoted well-organised actin filaments consistent with real muscle.

Conclusion:
This work is a first step in the development of functional 3D-bioprinted pulmonary ASM tissue with a modifiable stiffness. Ongoing optimization efforts will make our constructs more physiologically and disease relevant, allowing us to test the effects of pulmonary ASM stiffness in PPHN. This will help fuel the development of potential treatments for children suffering from PPHN.