GelMA microgels as a novel platform to promote pathophysiological vascularization in cardiac organoids

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Abstract

Cardiovascular diseases remain the leading cause of mortality worldwide, while physiologically relevant *in vitro* cardiac models have emerged to investigate disease mechanisms and promote regeneration *in vivo*. Currently, cardiac organoids fail to fully reproduce the hierarchical organization of native blood vessels and lack perfusable endothelial networks capable of efficiently delivering oxygen and nutrients, ultimately limiting tissue maturation and long-term viability and functionality. To address this challenge, this project proposes a microfluidic-assisted biofabrication strategy based on the endothelialization of gelatin methacryloyl (GelMA) microgels as modular vascular building blocks for cardiac organoid biofabrication. This preliminary study focuses on the optimization of microgel fabrication and the establishment of a robust endothelialization protocol. First, 7% and 10% w/v GelMA microgels were fabricated using a microfluidic platform and photocrosslinked with lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP). These were classified based on the Young's moduli. Then, human coronary endothelial cells were added to GelMA microgels. Finally, microgel coating by endothelial cells was followed over 14 days in culture. Our preliminary results show that the Young's modulus of 7% GelMA microgels equals to 8,07 ± 3,62 KPa, while the one of 10% GelMA microgels equals to 41,26 ± 6,89 KPa, which are reflecting the ones of physiological and pathological vessels, respectively. Both 7% and 10% GelMA microgels were efficiently endothelialized over 14 days, with minimal (non-significant) cell death. Future studies will evaluate the effects of the addition of these microgels within cardiac organoids to determine their potential to control pathophysiological vascularization. Conclusively, this modular biofabrication strategy may provide a novel, scalable platform for engineering vascularized cardiac organoids for cardiovascular disease modelling, drug screening, and regenerative medicine.