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Multiphysics three-dimensional model of a bioengineered haematopoietic platform for platelet production

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INTRODUCTION: Developing a practical strategy to produce platelets in vitro exhibits a growing interest in transfusion medicine and tissue engineering. In nature, platelets are made in the bone marrow haematopoietic niche by megakaryocytes, cells that protrude cytoplasmatic extensions into the lumen of bone marrow sinusoid capillaries. Here, the shear stresses generated by the blood flow allow the detachment of platelets which enter circulation [1]. Thus, a bioengineered haematopoietic model needs to mimic the 3D architecture, composition, and hydrodynamic environment of the native tissue.
METHODS: Our group used silk fibroin to fabricate a 3D porous scaffold that promotes platelet production by differentiated megakaryocytes in vitro [2]. The silk scaffold was implemented into the perfusion chamber of a milli-fluidic optically accessible bioreactor (MOAB) [3]. The perfusion rate of the bioreactor was predicted via a computational finite element multi-physics model carried out in a COMSOL®multi-physics platform, where the scaffold geometry was obtained with high-resolution images acquired using an X-ray micro-tomography scanner. Platelet production was quantified and analysed in terms of morphology and functionality. Additionally, megakaryocyte metabolism was evaluated during the platelet release process via FLIM analysis.
RESULTS: Thanks to the combination of interstitial perfusion and confocal optical accessibility, the bioreactor allowed complete control of the local conditions imposed on cells in terms of fluid dynamics and mass transport. Flow rates lower than 600 µL/min guarantee a shear stress distribution inside the culture chamber within the physiological range of 0-410 mPa [4][5]. Further, the pO2 predicted, ranges from 14 to 20% consistently with blood oxygenation in capillaries. Interestingly, real-time analysis of the metabolic profile showed that cells mainly rely on glycolysis at high shear stress, thus suggesting that fluid flow may influence cell function in an unexpected way.
DISCUSSION & CONCLUSIONS: Thus, the finite element model successfully predicted the distribution of oxygen gradient inside the bioreactor guaranteeing normoxic culture conditions and the shear stress at the fluid-cells interface for several values of perfusion flow rates. Our bioengineered haematopoietic niche, coupled with the computational model for prediction/monitoring/control, represents a promising candidate for producing platelets since the main physical, biochemical, and metabolic features of the platelet production process can be reproduced.
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