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Generation of 3D models of vascularized tissue in a millifluidic optically-accessible bioreactor

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INTRODUCTION: Unraveling the physiological reactions induced by biomaterials implantation is an essential requirement before clinical translation. Integration of tridimensional cell culture systems and computational studies can help modelling the behavior of living tissues [1]. By combining computational fluid dynamics (CFD) analyses with the use of a millifluidic optically accessible bioreactor (MOAB), suitable for dynamic culturing of cells in a microscopic tridimensional (3D) environment, we produced a quick and reliable technique for modelling vascularized tissue regeneration "in vitro".
METHODS: We fabricated 3D micro scaffolds consisting of two rows of nine microgrids, each of 500x500x40 µm, by 2-photon polymerization of the SZ2080 biocompatible photosensitive resin [2]. The geometry is a 3D micro grid characterized by pores of 50x50x20 µm3. We compared cell proliferation with/without micro scaffolds, and we investigated the system in perfused conditions, by comparing the micro scaffold to a flat glass coverslip at the bottom of the MOAB chamber. CFD analyses allowed to set-up optimal parameters for dynamic cell culture and shear stress values acting on cells cultured in the micro scaffold. Endothelial cells and fibroblasts seeded on glass coverslips and microstructures were imaged by confocal laser scanning microscopy (CLSM) for evaluating their proliferation rates and spatial organization. Specific growth factors (VEGF and TGF-β1) were administered for stimulating vessels formation.
RESULTS: CFD analyses were performed for determining the optimal flow rate (10 µl/min) for achieving a maximum shear stress value of 0.1 mPa inside the scaffold. CLSM imaging showed that microstructures do not affect cell viability. Cocultures proliferated both in static and dynamic conditions. Moreover, upon administration of growth factors, we observed the coculture reorganization starting from day 4.
DISCUSSION & CONCLUSIONS: CFD analyses allowed to evaluate optimal parameters for cell culture in perfused conditions. Experimental results show that the scaffold and bioreactor design supported endothelial cells and fibroblasts growth. Our culture system is a quick and reliable tool for modelling vascularized tissue regeneration "in vitro". Co-cultures are ongoing to quantify vessels and connective tissue formation. Administration of growth factors will be performed for understanding their cellular uptake/release kinetics.
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