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Optimization of the Nichoid microscaffold for the expansion culture of human adipose-derived mesenchymal stem cells

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INTRODUCTION: Adipose-derived mesenchymal stem cells (hADMSCs) are a promising resource for regenerative medicine, and they can be harvested directly from the patient with moderately invasive procedures and re-implanted without eliciting immune response [1]. Several clinical trials are active in phase II-III, but new technologies are requested to develop more efficient therapies. In this context, the micro-scaffold "Nichoid" has shown to induce pluripotency in stem cells, thanks to its peculiar 3D structure [2,3]. The aim of this study is to design, fabricate and validate a new geometry of the Nichoid, optimized for the expansion of hADMSCs and to investigate the mechanotransduction process of cells in different scaffold configurations, using a combined computational and experimental approach.

METHODS: We developed a computational model of the scaffold structural deformations caused by cell adhesion, using COMSOL Multiphysics and we designed a new "cubic" scaffold pore architecture that optimizes the mechanical stimuli exerted by the scaffold deformation on the adhering cells. Cubic Nichoids were fabricated by two-photon polymerization technique using a biocompatible photoresist as already described [4]. To validate the cubic Nichoid, we performed several biomolecular and bioinformatics analyses on hADMSCs expanded inside the scaffolds: a metabolic assay, RNA-sequencing, Real Time PCR, Western Blot, and immunofluorescence.

RESULTS: We predicted computationally the structural stability and the maximum deformation for several pore dimensions (10x10um, 20x20um and 30x30um). We identified the most suitable structure for hADMSCs as the one that maximized the isotropy of forces acting on cells. We observed a more roundish nuclei in cells cultured on the cubic Nichoid, with respect to traditional Nichoids. This corresponded to a higher expression of pluripotency genes induced by mechanical stimuli, also verified by the up-regulation of the stemness transcriptional core.

DISCUSSION & CONCLUSIONS: The cubic Nichoid recreated an ex-vivo physiological environment optimized for hADMSCs. This new scaffold demonstrates how engineering technologies can support regenerative medicine and in particular the clinical translation of stem cell therapies. Indeed, cells expanded in this new scaffold not only showed an increased maintenance of function, they could also be easily collected after expansion culture in view of an autologous transplantation and thus represent a valid therapeutic stem cell approach.

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