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Development of a bioprinted 3D model of aortic valve leaflet seeded with human valvular interstitial and endothelial cells

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Statement of the Problem: Calcific aortic valve disease (CAVD) is the third leading cause of cardiovascular disease being a progressive process, with initial valvular endothelium inflammation, followed by fibrotic thickening and extensive calcification of the valve leaflets. Currently, pharmacological interventions for slowing down the progression of CAVD are unavailable. Therefore, physiologically suitable *in vitro* models are required to study the cellular and molecular mechanisms of CAVD. Aim of this study is to obtain a 3D construct with a structure similar with the aortic valve leaflet.

Materials & Methods: Human valvular interstitial cells (VIC) were encapsulated in bioink and bioprinted. Printing was performed with the 3DDiscovery® platform (regenHU, Switzerland) and several bioink formulations. Valvular endothelial cells (VEC) were seeded on the construct surface. The constructs were maintained in culture for 7-21 days. Evaluation of viability of cells was determined using live/dead and MTT cell viability assays. Cell phenotype was analyzed by immunohistochemistry using phalloidin and specific antibodies.

Results & Discussions: In the current study, we obtained a 3D bioprinted construct with human VIC inside and a VEC layer on the top. Encapsulated VIC developed a well-defined cell network within construct and express low levels of alpha-smooth muscle actin (α-SMA) compared with VIC in bi-dimensional culture. The Western blot data indicated that bioprinted VICs have a less activated phenotype than those grown in bi-dimensional culture. VEC seeded on the constructs adhere, proliferate and form a monolayer at surface of the construct exhibiting endothelial specific markers: PECAM-1 and von Willebrand factor.

Conclusions: We have obtained 3D bioprinted constructs with valve leaflet structure, with viable VIC encapsulated in constructs and VEC on the surface. The obtained structure will help for further investigations of the dynamic interaction between valve interstitial and endothelial cells, in order to study the valvular disease progression and to develop potential therapeutic interventions.

Recent Publications

1. Cecoltan S, Stancu I C, Drăguşin D M, Serafim A, Lungu A, Ţucureanu C, et al. (2017) Nanocomposite particles with improved microstructure for 3D culture systems and bone regeneration. J Mater Sci Mater Med. 28(10):153.
2. C Deborde, D Simionescu, J Liao, L Sierad, C Wright and A Simionescu (2016) Stabilized collagen and elastin-based scaffolds for mitral valve tissue engineering. Tissue Engineering, Part A. 22(21-22):1241-1251.
3. Iordache F, Grumezescu A M, Maniu H and Curutiu C (2017) Development of Scaffolds for vascular tissue engineering: biomaterial mediated neovascularization. Curr Stem Cell Res Ther. 12(2):155-164.
4. Butoi E, Gan A M, Tucureanu M M, Stan D, Macarie R D, Constantinescu C, Calin M, Simionescu M and Manduteanu I (2016) Cross-talk between macrophages and smooth muscle cells impairs collagen and metalloprotease synthesis and promotes angiogenesis. Biochim Biophys Acta. 1863:1568-78.
5. Tucureanu M M, Rebleanu D, Constantinescu C A, Deleanu M, Voicu G, Butoi E, Calin M and Manduteanu I (2017) Lipopolysaccharide-induced inflammation in monocytes/macrophages is blocked by liposomal delivery of Gi-protein inhibitor. Int J Nanomedicine 13:63-76.

Biography

Elena Butoi graduated from Faculty of Physics, University of Bucharest and obtained her PhD in Biological Sciences in 2008 at ICBP-NS. Since 2014, she is Scientific Researcher Grade I at ICBP-NS and Head of Cell Adhesion Laboratory in the Biopathology and Therapy of Inflammation Department. Her group focuses on the effects of cross-talk between immune cells and vascular cells in progression of atherosclerosis and other cardiovascular disorders in normal or diabetic conditions. She has published more than 28 papers in ISI journals. Since 2017 she is involved in an interesting project aiming to uncover relevant diabetes-related alterations in aortic valves by developing *in vitro* 3D-printed model of aortic valve leaflet seeded with human valvular cells.

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