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3D Alginate Scaffold for Anatomical Aortic Valve Tissue Engineering

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Background

Within the field of biomedicine, alginate applications are numerous, from wound healing and cell transplantation to delivery of bioactive molecules. Recently, alginate based biomaterials are entering into clinical trials for the treatment of myocardial infarction (1). Due to its non-thrombogenic nature, this polymer is very promising for cardiac applications, including as scaffold for heart valve tissue engineering. One pivotal property of alginates in this respect is the possibility to form virtually any shapes (films, fibers, beads) in a variety of sizes. Alginate solutions can form gels in mild conditions in the presence of calcium, by displacement of sodium ions and resulting attraction of the alginate molecules. Our aim is therefore to fabricate 3 dimensional (3D) alginate scaffolds mimicking precisely the anatomical shape of human aortic valves, as a substrate for valve tissue engineering and repair (see Figure 1).

Methods

We used the gelling properties of alginate solutions to obtain scaffolds reproducing the complex geometry of aortic heart valves in a few easy steps. Briefly, the geometrical and structural design of a typical aortic heart valve (2–4) was obtained using Blender software (5). The generated 3D file was converted into stereo-lithography (STL) format and 3D printing performed in Objet Eden260VS - 3d printer (Stratasys, Edina, Minnesota, USA) using light-curable polyacrylate monomers. After printing the supporting material was removed manually which yielded flexible valve-like structure with sinuses of Valsalva and 3 coapting leaflets. Subsequently, agarose moulds were obtained by casting agarose saturated in CaCl2 solution (2% w/w) into the 3D printed form. Finally, alginate scaffold preparation was carried out by immersing the CaCl2-saturated agarose moulds into alginate solutions.

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Results

Calcium ions diffused from the agarose mould and effectively cross-linked alginate solution in close vicinity, resulting in an alginate gel layer. The agarose mould could be easily removed in a subsequent step. The resulting alginate structure closely matched the agarose mould geometry and hence the 3D printed replica of a human aortic valve. Moreover by extending the length of mould immersion into sodium alginate solutions, scaffold thickness and composition could be controlled. Such control allowed forecasting further improvement to facilitate cellularisation and tissue formation and to improve mechanical properties.

Conclusion

Alginate can form versatile and tunable hydrogels which can be cast in 3D configurations that mimic the shape of a human aortic valve. As preparation steps can be freely adjusted to incorporate viable cells, such structures could serve as basis for in vitro tissue formation, which would further improve mechanical properties of the hydrogel. In addition, the ease of chemical modification and functionalization of alginate with cell ligands provides rational tools to increase cell interactions and attract cells in situ, which are important steps in the formation of functional valves in vivo.

Overall, this novel and flexible technique that can be readily integrated with other strategies presents an important potential to create the “ideal” scaffold for producing a living valve substitute.

Figure 1. Alginate shaped in tricuspid valve, ventricular view (a), side view (b), hinge - atrial view (C), and open valve view (D). (Scale bars 1 cm).

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