3D BIOFABRICATION FOR TISSUE ENGINEERING

WOJCIECH ŚWIĘSZKOWSKI*

FACULTY OF MATERIALS SCIENCE AND ENGINEERING,
WARSAW UNIVERSITY OF TECHNOLOGY, POLAND
*E-MAIL: WOJCIECH.SWIESZKOWSKI@PW.EDU.PL

[ENGINEERING OF BIOMATERIALS 153 (2019) 6]

Introduction

Typical tissue engineering approach is to fabricate porous scaffold, and then to seed it with patient own cells and growth factors, before implantation. Difficulties with cell seeding and providing a proper 3D ECM-like environment for the cells are the main limitations of this approach. An innovative technique that may overcome current limits in reproducing complex structures of human tissues and organs is 3D biofabrication. This emerging fabrication technology relies on the simultaneous deposition of cells and biomaterials, mostly in a layer-by-layer fashion, to form 3D well-organized living heterogeneous porous structures that can mirror physiologically and morphologically relevant complex biological architectures. The aim of the study was to biofabricate biomimetic 3D models for tissue engineering of musculoskeletal tissues like muscle, tendon, or cartilage.

Materials and Methods

Innovative strategies to biofabricate biomimetic 3D models of musculoskeletal tissues, like cartilage, muscle, and tendon are presented. The 3D biofabrication approach is based on a microfluidic system coupled to a co-axial needle extruder for high-resolution computer-controlled 3D deposition of hydrogel fibers laden with different type of cells (FIG. 1a). In the first step formulations of ECM mimicking tailored hydrogel based bioinks were developed. Depending on application, the biomimetic hydrogels were composed of modified biopolymers like gelatin, alginate, hyaluronic acid, or PEG-fibrinogen. The gels were laden with different types of cells including bone marrow-derived human mesenchymal stem cells, muscle precursor cells or chondrocytes. Then 3D bioprinter and bioinks were used to precisely reproduce a 3D spatial organization of natural musculoskeletal tissues. The 3D printed advanced biostructures were cultured in static or dynamic conditions to develop into neo-tissues of musculoskeletal system.

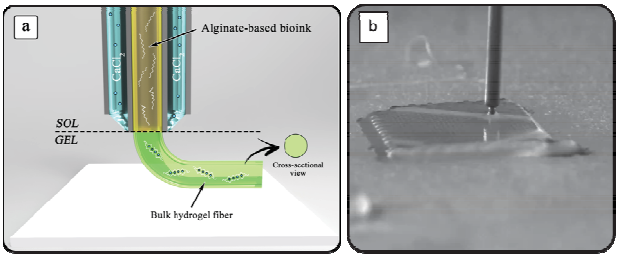

FIG. 1. Co-axial nozzle (a) for high-resolution 3D printing of hydrogel fibers (b).

Results and Discussion

By formulating tailored hydrogel based bioinks and precisely controlling the 3D spatial organization of the extruded hydrogel fibers, it was possible to biofabricate advanced engineered living constructs mimicking natural musculoskeletal tissues. The obtained with high resolution (~ 100 μm), a fiber-based 3D printed living constructs mimiced organized tissues like cartilage (FIG. 2a,b) [1], muscle (FIG. 2c,d) [2], and tendon (FIG. 2e) [3]. Furthermore, the mechanical loading and biochemical stimulation enhanced ECM deposition in 3D biofabricated constructs (FIG. 2f) [3].

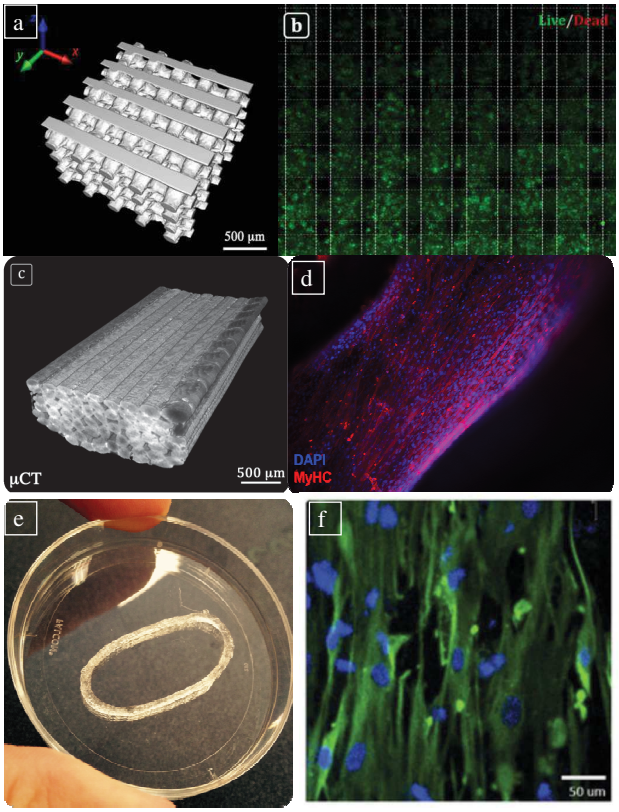

FIG. 2. 3D printed living constructs mimic organized tissues like cartilage (3D microCT image (a) and live-dead staining (b)) [1], muscle (3D microCT image (c) and immunofluorescence micrograph (d)) [2], and tendon (the ring of highly aligned, densely packed fibrous structures (e) and collagen I (green) expressed by hBM-MSCs encapsulated into the hydrogel yarns mechanically stimulated (f)) [3].

Conclusions

Properly designed bioinks and 3D biofabrication methods were crucial for development of 3D living constructs mimicking organized musculoskeletal tissues like cartilage, muscle, and tendon. Blending alginate with photocurable natural based polymers allowed to formulate ECM biomimetic inks that were used for high-resolution 3D microextrusion-based bioprinting a fiber-based 3D structures recapitulating architectures of native tissues. Additional post-processing biochemical and mechanical stimulation can induce MSC differentiation and enhance ECM deposition. In the next step, long-term in vivo evaluation of the biofabricated constructs are required before such tissue engineered products might be used in the medical practice.

Acknowledgments

This study was supported by Pol-Nor/202 132/68/2013 (NewJoint), STRATEGMED1/233224/10/NCBR/2014 (START), STRATEGMED3/306888/3/NCBR/2017 (ITE), and the subvention grant 2019.

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