Universität Basel

Research Project

Direct 3D Bioprinting strategies to study articular cartilage development and regenerative therapy for osteoarthritis

Third-party funded project

Project title Direct 3D Bioprinting strategies to study articular cartilage development and regenerative therapy for osteoarthritis
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By the year 2030, approximately 25% of the adult population is projected to suffer from clinically diagnosed osteoarthritis (OA). At present OA cannot be treated, but only the associated pain is managed by administration of anti-inflammatory drugs. Implantation of tissue engineered cartilage in the affected lesions has been a hotly pursued research area worldwide for last three decades. However, this line of research has not succeeded so far. The most common problem encountered is that the engineered cartilage generated using mesenchymal progenitor cells (MSCs) does not share the molecular properties of native permanent cartilage but, instead, become vascularized, undergoes hypertrophic differentiation and eventually is replaced by bone once implanted in vivo. These latter features characterize both the transient cartilage (i.e.; cartilage formed at the epiphyseal growth plates of long bones) and the articular cartilage in OA joint. The overall objective of this proposal is to engineer a cartilage tissue which will be molecularly indistinguishable from healthy articular cartilage and which remains phenotypically stable also when implanted in a OA environment. We propose a comprehensive plan to achieve this, at the core of which is to engineer developmental processes in order to control fate specification by MSC and developing functional cartilage tissue construct by 3D bioprinting.Working hypothesis. Most of the tissue engineering studies did not take into account: (i) the natural process of permanent cartilage differentiation; (ii) the molecular niche in native permanent cartilage and the changes it undergoes during OA; (iii) the nature of the engineered cartilage; (iii) the effect that the niche, particularly the altered one in OA, has on tissue engineered cartilage. In the current proposal, we will develop a comprehensive strategy for designing a disease modifying therapy of OA, combining our strengths in 3D bioprinting, biomedical engineering, microfluidics and joint cartilage developmental biology. We hypothesize that phenotypical stable cartilage can be engineered by culturing MSC with signalling proteins (i.e.: Wnt ligands) and morphogenetic inhibitors (BMP inhibitors) recently shown (mainly by the applicants) to be key in regulating differentiation of MSC into stable or transient cartilage. Specific aims & experimental design. The first aim is to generate 3D bioprinted permanent cartilage in vitro. For this purpose, we will initially perform a screening of different doses and temporal stages of supplementation of Wnt ligands and BMP inhibitor within a microfluidic platform allowing generating and perfusing 3D MSCs microaggregates. This will allow identify the most promising conditions enabling the differentiation of MSCs into stable cartilage, to be scaled up and applied into the 3D bioprinted constructs. We will then explore use of silk-gelatin bioink tethered pathway-regulatory molecules on differentiation of the encapsulated mesenchymal cells (Aim 1). Once this is achieved, we will work towards two distinct but complementary approaches: (i)

We will develop an in vitro model for OA. For this we will activate BMP signalling in the 3D bioprinted permanent cartilage to investigate if it recapitulates changes associated with OA. This will allow us to create a platform for rapid screening of drugs or other bioactive molecules which may be therapeutically relevant (Aim2). We will then develop bioink which will be either sensitive to matrix metalloproteases or mechanical stimulation to release in situ BMP inhibitors to protect the 3D bioprinted permanent cartilage once implanted in an OA joint (induced in mice), environment which would instead promote transient cartilage differentiation (Aim 3).Expected value of the proposed project. Even after 30 years of efforts, fabrication of load bearing and clinically relevant, biochemically equivalent cartilage tissue constructs still remains elusive. We are aware that this is a novel and highly ambitious objective, but collectively we have the necessary expertise and insight to attempt this, which if achieved will surely be a major boost for developing a disease modifying therapy for OA.

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