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Biofabrication

EDITORIAL

Editorial: Special Issue on biofabrication of cartilage, bone and their interface

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The osteochondral interface is a fascinating construct of nature which contributes to the functioning skeleton, but also is susceptible to injuries and pathologic changes during arthritic diseases. Healthy osteochondral tissue exists as a functional gradient between two highly specialized, but very different connective tissues, bone and articular cartilage. The mechanisms which allow these two tissues to coexist in close proximity, while maintaining key differences in oxygen, vascularization, biophysical properties, transport mechanisms and regenerative capacity, are still being explored. Biofabricated models of the OC interface can play a key role in deciphering these mechanisms. The same biofabrication tools also have the potential to transform how we treat the osteochondral (OC) unit following injury or disease.

This special issue on 'Biofabrication of cartilage, bone and their interface' highlights recent advances in orthopedic applications which harness the power of bioprintable materials and emerging biofabrication platforms. The special issue covers new formulations of biomaterials for the engineering of both chondrogeneic and osteogenic tissues, and highlights approaches to promote distinct tissue types. As an example, Kilian *et al* presents a coaxial extrusion approach where a chondrogenic growth factor (TGF-β3) and an osteogenic growth factor (BMP-2) are ensconced in a Laponite core which is surrounded by a hydrogel shell of alginate-methylcellulose [1]. The local delivery of growth factors from the core was found to stimulate cell differentiation in the shell. In a similar vein, Terpstra *et al* modulated the degree of blood vessel invasion into bioprinted constructs by incorporating either proangiogenic factors (collagen 1 fibers) or anti-angiogenic factors (decellularized cartilage microfibers) into their fibrin-based bioink [2]. These materials were explored in an osteochondral model [1] and a meniscus model [2] respectively, the latter characterized by both vascularized fibrous cartilage and avascular hyaline cartilage regions.

Bottom-up approaches for biofabrication of tissues have gained considerable attention of late. In particular, microgel-based granular materials can help to overcome the nutrient transport challenges associated with growing large tissues. The enhanced mass transport offered by the void compartment of granular materials was shown to be important by Flegeau *et al*, who demonstrated both the printability and biocompatibility of tyramine-functionalized hyaluronan microgels and chondrocytes [3]. In a related approach, Cui *et al* have used microgels containing umbilical cord-derived mesenchymal stromal cells (MSCs) to assemble osteochondral tissues [4]. Chondrogenic microspheres containing heparin and osteogenic microspheres containing strontium nanoparticles were pressed into a polycaprolactone (PCL) printed scaffold to allow formation of the two distinct tissue layers.

Other contributions highlight the importance of materials which counteract oxidative stress in order to successfully treat cartilage defects *in vivo*. Shi *et al* developed hyaluronan hydrogels with interesting reactive oxygen species scavenging properties [5]. Their system works by incorporating a dynamic boronate ester bond which could scavenge H_2O_2. This reversible bond was also thought to contribute to the favorable rheological properties for extrusion printing and injectability. Galarraga *et al*, on the other hand, used norbornene-modified hyaluronan gels of varying stiffness to understand how the properties of the cell carrier regulate cartilage development and maturation *in vitro* [6]. They found that initially softer hydrogels (2 kPa) significantly enhanced cartilage formation by MSCs compared to stiffer gels. They also demonstrated that the soft hydrogels could be reinforced by meshes produced by melt electrowriting. Wang *et al* also considered the challenge of engineering mechanical functional cartilage, using 3D printed poly(lactide-co-ε-caprolactone) to reinforce highly porous alginate scaffolds, leading to the

development of highly elastic implants with bulk mechanical properties comparable to the native tissue [7]. Furthermore, they observed that functionalization with a sulfated glycosaminoglycan mimic supported the sustained release of TGF-β3, potentially enabling their use as 'off-the-shelf' implants for joint regeneration.

Emerging biofabrication strategies can also facilitate the engineering of heterogenous constructs that mimic the transition from articular cartilage to bone that characterizes the OC unit. Recognizing this, Beeren *et al* explored if the introduction of peptides on the surface of printed polymer scaffolds could enhance the chondrogenic or osteogenic differentiation of human MSCs [8]. Using a novel extrusion-based additive manufacturing (AM) technology, they were able to generate a gradient of functional groups across the scaffold. As opposed to the spatial presentation of peptides or growth factors for engineering the OC unit, Celik *et al* explored the 3D bioprinting of microRNA (miR)-transfected adipose-derived stem cell (ADSC) spheroids to produce interfacial tissues [9]. The delivery of miR-148b was found to support osteogenic differentiation, while the codelivery of miR-140 and miR-21 supported chondrogenesis. Using aspiration-assisted bioprinting, these spheroids were then be used to engineer a dual-layer construct with distinct osteogenic and chondrogenic zones.

The regeneration of large musculoskeletal defects remains a significant challenge. Many scaffolds that possess appropriate bioactivity lack the mechanical properties for use in large, load-bearing defects. Dewey *et al* assessed the capacity of mineralized collagen scaffolds reinforced by 3D printed PCL meshes to support healing in a critically sized porcine craniofacial bone defect model [10]. While successful healing was limited, the results point to areas for targeted improvement in large bone defect healing. Preserving bone structure is also important in the regeneration of OC defects. Zlotnick *et al* fabricated thick-shelled microcapsules containing the pro-osteogenic agents, and delivered these microcapsules in a large animal model of osteochondral injury [11]. These microcapsules were designed to rupture under mechanical load, enabling the controlled release of their therapeutic cargo at the defect site, which was found to preserve local bone structure within the OC unit.

Also in the field of bone regeneration, Touya *et al* assessed the potential of laser-assisted bioprinting in a critically sized murine calvaria bone defect model [12]. While a collagen-mineral ink was found to support early osteogenesis *in vitro*, complete healing was not observed *in vivo*, pointing to the need for further ink improvements. Kang *et al* sought to address the challenge of improving the angiogenic and osteogenic potential of their 3D printed scaffolds through functionalization with ADSC derived exosomes [13]. The inclusion of such exosomes was found to improve cell attachment and proliferation on the scaffolds *in vitro*, as well as enhancing vascular invasion and bone formation *in vivo*. Alternative materials might also help in the development of novel bone graft substitutes. Porous magnesium (Mg) is a promising biodegradable scaffold material for treating critical-size bone defects, but can be challenging to process using traditional AM technologies. Xue *et al* demonstrated that 3D weaving of Mg wires represents a high throughput manufacturing method, enabling the production of scaffolds that can be optimized for stiffness, porosity and topology [14].

A recent linguistic analysis identified the biofabrication of osteochondral tissues as a growing field of research in the field of orthopedics [15]. We hope that this special issue highlights many of the important advances that have been made in the field of biofabrication that are enabling the engineering of OC-like tissues. This series of papers also highlights many of the outstanding challenges in the field, which will hopefully stimulate exciting new research projects in the years ahead.

Data availability statement

No new data were created or analyzed in this study.

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