3D Bone Bioprinting

Subjects: Others

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Every year, approximately a couple of million bone grafts are performed worldwide to treat bone lesions, of which about 1 million only in Europe, thus bone regeneration is necessary to replace the damaged tissue, while the improvement of bone healing, both qualitatively and quantitatively, is mandatory. Bone tissue is constituted by cells with functions carefully coordinated, and a complex cross-talk between bone forming and inflammatory cells is known to guide successful regeneration, thus repairing bone is not an easy task. Autografts are still considered the gold standard for repairing bone defects, although they are not without significant drawbacks, such as donor site availability and possible morbidity. To overcome the pitfalls of grafts, researchers relied on bone tissue engineering (BTE) and 3D bioprinting techniques to produce cell-laden scaffolds, in which bone biological components are assembled to form a 3D environment. Several techniques of bone bioprinting have been developed: inkjet, extrusion and light-based 3D printers, which use different bioinks, i.e., the printing materials.

Keywords: 3D Bioprinting, Bone, Regenerative Medicine

1. 3D Bioprinting

3D bioprinting is a cutting-edge technology with a broad utility in bone tissue engineering (BTE) and regenerative medicine (RM) [1][2]. It is used to build constructs starting from a single cell type using layer-by-layer deposition of specific bioinks, which are essentially the biological components needed for the scaffold. Therefore, 3D bioprinting allows to develop highly reproducible, spatially controlled structures made of different materials, growth factors and cells, such as synthetic bone substitutes.The great advantage of 3D bioprinting relies in the potentiality to spatially distribute the cells within the solid or semi-solid biomaterials, thus optimizing tissue regeneration [3]. The development of 3D-bioprinted bone tissues is of great relevance and impact on clinical practice, because it also allows the reconstruction of bone defects with complex shape, just by translating computed tomography (CT) or microCT data of defects to printable image of them, leading to patient-specific implants [4][5][6]. The ideal scaffold should resemble a 3D structure and composition of human bone, it has a resorption rate that gives time to the bone from the recipient site to replace it, it provides nourishment of the graft cells and allows vascularization, which is essential for the graft success and a higher bone healing ability compared to non-osteoinductive ceramics [7]. Moreover, 3D bioprinting allows the production of constructs with different geometrics, porosity, and sizes, which are features relevant to obtain more osteoinductive scaffolds. Generally, osteoblasts or progenitor cells need a proper stimulation by bone morphogenetic proteins (BMPs) [8] for osteogenic differentiation, but some biomaterials, such as calcium phosphate (CaP) ceramics can induce an intrinsic osteoinduction, where mesenchymal stem cells (MSCs) differentiate into osteoblasts, even without exogeneous BMPs, avoiding the adverse effects of BMPs treatment [9][10][11][12].

Bioinks

Bioinks are the key components of bioprinting technology; they include printable organic and inorganic materials, biological factors and other components that enhance cell growth, differentiation and preserve shape fidelity during free-form deposition as extruded filaments [13][14][15][16]. Bioinks useful to obtain effective bone substitutes require properties including biocompatibility, biomimicry, biodegradability, bioprintability and mechanical integrity [17][18]. Thus, the design of the appropriate bioink is probably the main challenge of bioprinting [19][20]. Importantly, bioprinting of bone requires the use of bioinks capable of transitioning from a liquid state to a gel structure, without compromising cell viability and bioactivity [6]. Since bone is exposed to different and not uniform mechanical stress, and to various nutritional and vascular needs, bioinks must possess physical properties providing aid for cell differentiation by ensuring a favorable 3D microenvironment [21]. Starting from the introduction of cross-linkable bioinks, such as methacrylated gelatin and hyaluronan, more and more new materials are being engaged to make optimized bioinks. Another approach relies on the use of composite materials, which combine the advantages of each bioink, improving their mechanical strength, printability, biocompatibility, and gelation characteristics [22][23][24]. Macrostructural and geometry properties of material have a deep impact on the effectiveness of a scaffold, because porous materials, characterized by numerous pores of

variable size and connectivity, are suitable for the passage of oxygen, nutrients, and cellular wastes. Notably, the porosity of the cell-laden scaffold is known to affect tissue formation and concomitant angiogenesis, which are two critical aspects for BTE [25][26][27]. Tarafder et al. [28] showed in a rat model that the control of the pore size resulted in an increased compressive strength, cell density, biocompatibility, and osteogenesis [28]. Various scaffolds based on different bioactive nanomaterials have been tested for their capabilities to induce new bone formation. For instance, hydroxyapatite (HA) nanoparticles showed a favorable osteoinductive activity on MSCs. In particular, HA nanostructured with concave macroporosity, derived from CaP crystals, accelerate osteoinduction, since they are chemically and structurally similar to those of the natural bone tissue [29]. Other nanoparticles made by different components, such as molybdenum-doped bioactive glass [30], magnetic iron oxide [31], strontium containing bioactive glass [32], and gold [33] showed osteoinductive abilities. Depending on the final aim, the cells can be deposited onto the scaffold biomaterial during the printing process, generating the scaffold-based bioinks [19] or, alternatively, they can be directly printed embedded in the biomaterial, implementing the scaffold-free bioinks [34][35][36].

2. 3D Bioprinting Applications to Treat Bone Defects

Besides BTE, 3D bioprinting is strongly relevant in the field of cancer research, where 2D tumor models do not reconstitute the complexity of the dynamic tumor microenvironment [37]. Conversely, 3D-bioprinted models allow for reproduction of cell–cell and cell–matrix interactions and have the advantage to integrate a vascular system to study tumor angiogenesis [38]. Hence, the tumor tissue should be placed within a bioprinted vascularized parenchyma to analyze how cancer cells grow and other carcinogenic events, i.e., intravasation and extravasation [39]. Important to note is that a 3D biomimetic bone matrix has been used to create a model of breast cancer bone metastases, with a bone like microenvironment that provides cross-talk among breast cancer cells, human bone marrow MSCs, and osteoblasts [40]. Zhu et al. [41] used a 3D printed nano-ink, made of hydroxyapatite nanoparticles suspended in hydrogel, to simulate a bone-specific environment to study breast cancer bone invasion.

The potential applications of BTE in orthopedics are enormous since can solve both bone and cartilage problems [42]. A comprehensive review analyzing the application of BTE for orthopedic trauma according to the different anatomical sites, showed its usefulness to treat bone trauma in a patient-specific manner [43]. Alba et al. [44]developed a new method to engineer periosteum tissue by printing periosteal derived cells (PDCs) mixed with alginate on collagen scaffolds. The presence of collagen contributed to maintain the structural integrity and osteogenic differentiation of PDCs, which was demonstrated by osteocalcin and alkaline phosphatase gene expression.

A multi-component bioink, constituted by wood-based nano-cellulose and bioactive glass to strengthen gelatin-alginate bioinks, was tested and resulted effective in sustaining bone cell viability, proliferation, and osteodifferentiation [44].

Cartilage tissue defects are difficult to repair due to cartilage poor self-repairing capacity, thus the potential to re-create functional articular cartilage by 3D bioprinting is contemporary tempting and challenging. Cartilage must sustain heavy loads, therefore a hybrid scaffold, constituted by PCL with rabbit chondrocytes and fibrin collagen hydrogel, was fabricated to enhance mechanical and biological properties for load-bearing cartilage. The authors showed that this hybrid construct formed cartilage-like tissues both in vitro and in vivo, as evidenced by the deposition of type II collagen and glycosaminoglycans [45]. Daly et al. [46] used an MSC-laden bioink (arginine-glycine-aspartic acid (RGD)-modified alginate hydrogels) co-deposited with PCL fibers, which showed s 350-fold increase in compressive modulus of bioink/PCL templates. The constructs had the potential to be implanted as vertebral bodies in load bearing locations.

O’Connell et al. [47][48] developed a device named “Biopen”, which is basically an EBB bioprinter for in vivo application directly during the surgery. This Biopen was utilized to repair chondral defects in a large animal ovine model [49]. Repairing an osteochondral defect remains the most challenging part of engineering implants for full thickness osteochondral lesions, which can be repaired through a modular tissue assembly strategy, according to Schon et al. [50].

Furthermore, 3D-printed tissue models may be used to test the efficacy and toxicity of new drug candidates mimicking the native tissue, thus fostering translation of new therapeutic molecules into clinics [51][52]. Compared to other types of 3D in vitro systems [53], 3D bioprinting has numerous advantages such as the controllability, the high-throughput capability, and the generation of drug-delivery vehicles precisely [54]. Indeed, the DVDOD technology delivers droplets to a specific location in a volumetric manner with a high-throughput capability. This technique has been tested to bioprint pre-osteoblast cells with alginate hydrogel into bone damaged tissue, in a minimally invasive manner, showing the formation of functional tissue [55].

Recently, a 3D bioprinted pseudo-bone drug delivery scaffold for simvastatin was generated to promote bone healing. This scaffold displayed matrix strength, matrix resilience, and porous morphology of healthy human bone [56].

In another work, 3D printed PCL/hydrogel composite scaffolds, loaded with bioactive small molecules (i.e., resveratrol and strontium ranelate) able to target bone cells, have been generated and studied to treat craniomaxillofacial defects. The authors implanted the 3D printed scaffolds, with and without small molecules into a rat model with a critical-sized mandibular bone defect, demonstrating that the bone scaffolds, carried with small molecules, showed enhanced angiogenesis, inhibition of osteoclast activities, and stimulation of MSC osteogenic differentiation with consequent in vivo mandibular bone formation eight weeks after implantation [57]. In Table 2, we present some works potentially relevant for their clinical implications, where 3D bioprinting resulted as useful in repairing bone defects.

Table 2. Applications of 3D Bioprinting on bone defects.

Cell Types, Molecules	Bioink	Bioprinting Modality	Application
Bone marrow MSCs, osteoblast	GelMA + nanocrystalline HA [40]	LBB (Stereolithography)	Breast cancer bone metastases
Osteoblast, breast cancer cells	PEG hydrogel + nanocrystalline HA [58] Hydrogel resins (PEG, PEG-diacryilate) [41]	LBB (Stereolithography)	Breast cancer bone metastases
Without cells	(PLA) and acrylonitrile butadiene styrene (ABS) [57]	EBB with Fused deposition model (FDM)	Radius fracture repair
Periosteal derived cells	Alginate hydrogel + collagen I, II [44] [59]	EBB by piston-driven system	Periosteum Tissue Engineering
MSCs	RGD alginate hydrogels [46]	EBB by multiple-head 3D printing system	To engineer endochondral bone
ASCs	HA-GelMA [49][50]	EBB by Biopen	Regeneration of chondral lesions
Meniscal fibrochondrocytes (MFCs)	meniscus extracellular matrix (MECM)-based hydrogel [60]	3D printing fused deposition modeling	Meniscus regeneration
IPS cells, 143B human osteosarcoma cells, preosteoblasts MC3T3	Alginate hydrogel [55]	Direct- volumetric Drop-on-demand (DVDOD) technology	Microtissue fabrication and drug delivery
Simvastatin	copolymeric blend of polymers: polypropylene fumarate (PPF), PEG-PCL-PEG, and pluronic PF 127 [56]	LBB	Drug delivery
Resveratrol and strontium ranelate	PCL/hydrogel [57]	EBB	Cranio-maxillofacial regeneration

3. Conclusions and Remarks

Even though clinical application of bioprinting technology is still in its infancy, the production of entire and functional organs characterized by relevant dimensions is an attractive challenge in TE. As portrayed before, to get closer to this ambitious goal, several aspects should be considered, such as a functional and hierarchical organized vascular network integrated in the system and the incorporation of the various cell types involved in the organ biology [61][62]. Bone may become paradigmatic in this process, as it seems to be more ahead than other tissues in its way toward clinical application. Significant progress has been made in 3D bioprinting for BTE, combining biomaterials, cells, and factor to obtain engineered bone tissue grafts, able to promote bone regeneration. For instance, bioprinted bone was successfully implanted in pre-clinical models [63] and 3D-printed plastic, ceramic, or metallic implants for bone tissue replacement [62] have been successfully transplanted into humans. Finally, a recent work demonstrated a unique case of transplantation of a 3D-printed bio-resorbable airway splint into an infant [64].

The exponential interest in these technologies is leading multidisciplinary teams to develop new bioinks [19] and post-printing procedures. Indeed, thanks to new self-absorbing polymers and the correct incorporation of specific molecules, mechanical, structural, and biocompatibility properties of these materials will be increased to recreate a correct milieu.

The other great technological challenge will be played in the management of post-printing procedures. In fact, more and more companies are developing different types of bioreactor, both in the field of millufluidics and microfluidics. Correct metabolic management and mechanical stimuli of BTE will therefore be possible.

In conclusion, considering the fast evolution of technology, in the next decade it is plausible to expect that volumetric composite tissues with native tissue-like properties will become printable. Indeed, the development of advanced high-resolution bioprinters with multiple modalities and print-heads (such as the newly created ITOP [65]), will lay the foundation for creating complex heterocellular and vascularized tissues. In this regard, the recent development of 4D bioprinting technology [66] could play a key role, since the integration of the concept of time with the 3D bioprinting technology will permit the development of tissues with high levels of complexity and size [67]. This aspect is particularly relevant since natural tissue regeneration is subjected to dynamic modifications of macro-/micro-structures and composition due to different intrinsic and external stimuli. Thus, a sort of maturation and functionalization of the 3D-bioprinted tissue with time is necessary and can be achieved by 4D bioprinting technology [68].

The technological complexity in these fields will make the need for laboratories with extremely multidisciplinary skills increasingly evident. Moreover, standardized regulatory protocols will need to be established, above all considering the even more increasing necessity to translate into clinical practice the use of these TE products.

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