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Editorial Open Access

3D Printing of Bioactive Ceramic Scaffolds for Bone Tissue Engineering

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Editorial

Bone tissue engineering has emerged as an innovative and promising strategy for treating bone defects, in which a three-dimensional (3D) porous scaffold is loaded with tissue-inducing factors or specific cells to launch a tissue regeneration in a natural way [1,2]. A variety of materials, consisting of bimetallic materials, bioceramics, biopolymers or bio composites, have been proposed and used to fabricate scaffolds for bone tissue engineering over the last few decades, while the functions similar to natural bone remains a challenging task [3]. Architecture, mechanical property and osteogenic ability are considered as the most critical characteristics for an ideal scaffold [4]. Many bioceramic materials have high stiffness and bioactivity (i.e., their similarity to the mineral phase of natural bone) [5,6], which can act as a temporary framework for providing a suitable environment for cell adhesion, growth, and more explicitly help bone tissue regeneration. Bioceramics refer to a class of ceramic materials with specific biological or physiological function, and can be used directly in the human body or in applications related to the human body [7].

Scaffold is a 3D biocompatible structure that can mimic the properties of mechanical support, cellular activity and protein production through biochemical and mechanical interactions. Also, 3D scaffold provides a template for cell attachment and stimulates bone tissue formation *in vivo* [8,9]. Currently, there is an intensive concerning on the development of fabrication methods for enhancing the function of scaffolds. Traditional or regular methods to fabricate 3D porous scaffolds, such as particle leaching, foaming, or freeze-drying, have limitations to precisely control the overall architectures and internal pore connectivity [10,11]. Advanced additive manufacturing techniques, such as 3D printing, can control the architecture and pore structures precisely and produce custom-designed, computer-controlled tissue scaffolds, overcoming many limitations of current fabrication methods [12].

To date, much effort has been made to fabricate bioactive ceramic scaffolds by 3D printing techniques, and show great application promising in bone tissue engineering. A wide range of bioactive ceramics, such as hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), bioactive glass (BG) and calcium silicate (CS), similar in composition to the mineral phase of bone are of great clinical interest [13]. Bioactive ceramic scaffolds could be implanted into bone defects and self-degrade *in vivo*. Importantly, bioactive ceramic scaffolds are able to react with physiological fluids, resulting in the formation of strong chemical-force bonding to bone tissues due to the formation of bone-like HA layers [14,15]. Nowadays, a variety of studies has reported on the relationships among the chemical compositions, bioactivity and the fabrication process of scaffolds, modification and so forth.

To date, 3D printing of pure bioactive ceramics has gained much progress. However, the development of composite inks quickly emerged as the technology grew, especially due to the development of direct ink writing printer. The main goal of using composite inks is to enhance ink properties such as process ability, printability, mechanics (stiffness) and bioactivity (to enhance cellular function and tissue integration) [16]. HA, β-TCP, BG and CS are widely used as the inorganic biomaterials due to their excellent osteoconductivity [17]. Polymeric biomaterials used for bone tissue engineering applications are usually biocompatible polymers (such as poly(lactic acid) (PLA), polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA)) or natural hydrogels (such as collagen, chitosan and alginate) [18]. Much progress has been achieved on bioceramic/polymer composite scaffolds, bioceramic/hydrogel composite scaffolds, and multifunctional bioceramic-based scaffolds.

The advantage of biodegradable bioceramic/polymer composite scaffolds is that altering the organic/inorganic material composition or ratio can change the properties of the composite scaffolds to satisfy the requirements for bone tissue engineering. PLA, PCL, PLGA and so on are common biocompatible polymers used for bone tissue engineering applications. Also, these biopolymers can act as binders during the printing process. For example, Adam et al. [19] 3D-printed a new synthetic osteoregenerative biomaterial, hyperelastic "bone" (HB), which is composed of 90 wt% HA and 10 wt% PCL or PLGA. The resulting 3D-printed HB exhibited excellent elastic mechanical properties (~32 to 67% strain to failure, ~4 to 11 MPa elastic modulus). Beyond these, HB became vascularized, quickly integrated with surrounding tissues, and rapidly ossified and supported new bone growth without the need for added biological factors when implanted *in vivo*.

Hydrogels are three-dimensional polymer networks that can provide excellent "soft material" systems to mimic native extracellular matrix (ECM) microenvironments due to their tunable degradation, mechanics and functionality [20]. Extrusion-based 3D printing systems are the most suitable methods to print bioceramic/hydrogel composite scaffolds. The classical approach to design bioceramic/hydrogel composite scaffolds is to formulate a hydrogel solution firstly and incorporate ceramic powders into the hydrogel matrix that forms a network immediately after printing. The network could be physically or chemically cross-linked in response to an external stimulus (*i.e.* light, temperature, or ion concentration) [21]. Common hydrogels for 3D printing are made from natural polymers such as alginate, gelatin, agar, cellulose, collagen, silk fibroin, hyaluronic acid, or from synthetic polymers such as poly(vinyl alcohol) (PVA), polyacrylamide, poly(ethylene glycol) (PEG), or a synthetic-natural mixture.

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Generally, the hierarchical structure, surface and interface of biomaterials are important factors that influencing their biological properties. Bioactive ceramic scaffolds have been widely used for bone tissue engineering by optimizing their chemical composition and pore structure. Importantly, bioactive ceramic could be modified with various functional materials, and a variety of functional scaffolds have been developed for bone tissue engineering.

Many reports are there on the modification of bioactive ceramic scaffolds to achieve sustained drug delivery. For example, porous HA scaffolds were developed by coating rhBMP-2-delivery microspheres with collagen [22]. The coating of rhBMP-2/collagen microspheres facilitated the adhesion of hMSCs, and the scaffolds can simultaneously achieve localized long-term controlled release of rhBMP-2 and bone regeneration, which provided a promising route for improving the treatment of bone defects.

For the treatment of bone defects caused by malignant bone tumors, functional 3D porous scaffolds that function in both tissue regeneration and tumor therapy are expected to address this need. Now, some functional materials were incorporated or combined with bioactive ceramic scaffold to fulfil more functionality, such as magnetic hyperthermia and photo thermal therapeutic properties. Yang et al. [23] 3D printed bioactive glass scaffolds and functionalized them with black phosphorus (BP) nanosheets, the *in situ* phosphorus-driven, calcium-extracted bio mineralization of the intra-scaffold BP nanosheets enables both photo thermal ablation of osteosarcoma and the subsequent material-guided bone regeneration, which provides a feasible countermeasure for efficient localized treatment of osteosarcoma.

In summary, the shapes of bone defects caused by trauma, tumors or disease are often irregular. Together with modern imaging and computer aided manufacturing technologies, 3D printing can fabricate special shaped scaffolds rapidly and conveniently, which has greatly advanced the progress of bone tissue engineering. Further developments in 3D printing of bioactive ceramic scaffolds for bone tissue engineering will require scaffold design optimization, better knowledge of cell and organ physiology and most importantly, new bioactive ceramics that can be 3D-printed and also emulate the compositional, structural, and functional complexities of human natural bone.

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