Biomimetic Scaffolds for Bone Tissue Engineering

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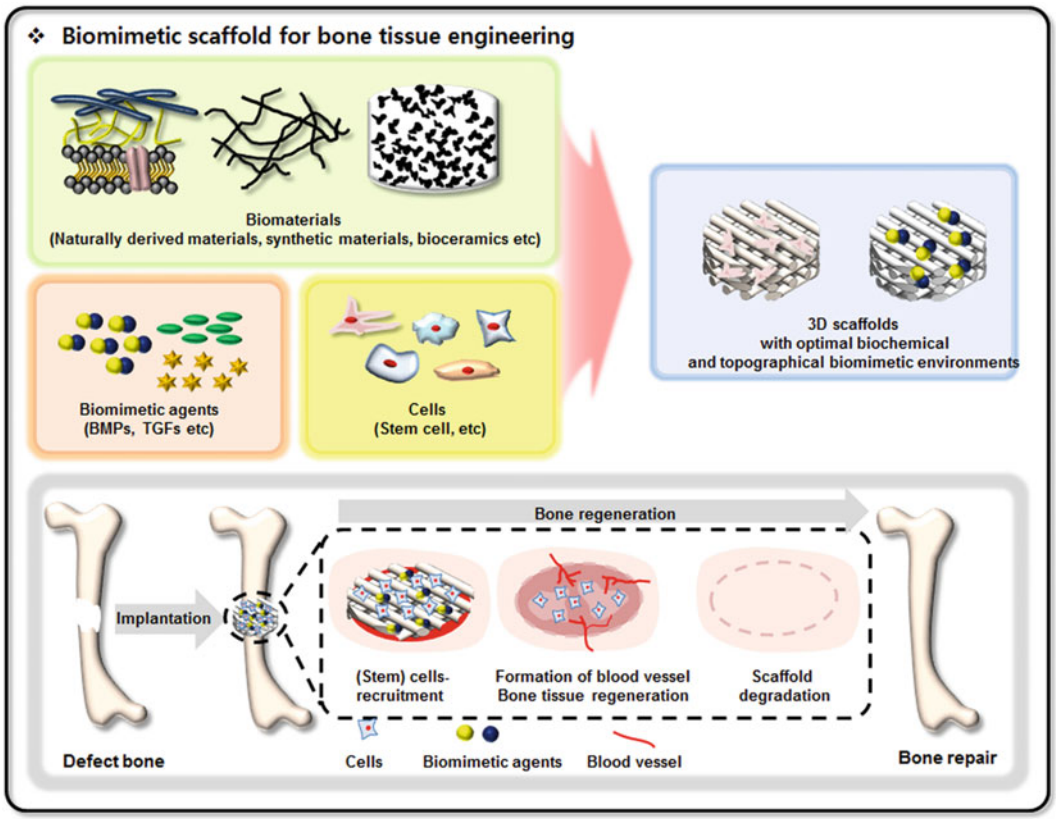

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7.1 Introduction

Tissue regeneration in living organisms is mediated by biologic regulatory factors that promote tissue renewal, restoration, and growth (Ceafalan and Popescu 2016). Scaffolds are important tools used in tissue engineering for the regeneration of lost or damaged tissues.

From the biological point of view, scaffolds should support the in vivo development of an extracellular matrix in sites of lost or damaged tissues (Kim et al. 2011). In addition, scaffolds should allow influx of nutrient substances from the surrounding tissue or biologic medium and the exit of waste formed in the tissue. Thus, scaffolds should create unique opportunities to regenerate tissues.

Biomimetic scaffolds can be formed using materials that have been designed to elicit specified cellular responses mediated by regulatory factors inside of the engineered environments (Chen et al. 2016). Biomimetic scaffolds are formed into three-dimensional (3D) architectures suitable for cell seeding and cultivation. With biomimetic scaffolds, (stem) cells can be cultivated or differentiated at the right time, in the right place, and into the right phenotype. Biomimetic scaffolds, particularly, are guided by the need to restore cell signaling and match the mechanical behavior of the tissue being engineered (Huang et al. 2016). Additionally, the biological agents inside of biomimetic scaffolds should serve as templates for cell growth and provide significant control over the cellular environment to manipulate cellular processes (Monteiro and Yelick 2017).

Biomimetic scaffolds can be used to closely mimic the generation of authentic tissue, which represents the environment of cells in a living organism, while enabling tight control over the cell environment and cellular processes (Skylar-Scott et al. 2016). Biomimetic scaffolds can be manufactured for precise control of patterning and mobilization of biological agents such as ligands, hormones, and cytokines (Moeinzadeh and Jabbari 2015).

Bone, a tissue containing a dense mineralized matrix, can withstand significant compressive loads (Tracy et al. 2016). Although bone has the innate ability to repair and regenerate, various clinical bone graft procedures are employed in orthopedic and craniofacial medicine (Kashte et al. 2017; Park and Park 2016; Gentile et al. 2017; Lee et al. 2017a). Autologous bones are common, but allografts, xenografts, and alloplast grafts have also been widely utilized.

From the mechanical point of view, biomimetic scaffolds for bone regeneration must bear external loading and provide the shape to the tissue that is to be regenerated (Tatman et al. 2015; Domingues et al. 2016; Behzadi et al. 2017; Lee et al. 2017b). Thus, biomimetic scaffolds for bone regeneration require mechanical stability to support the needed geometry, along with large interconnected pores for cell infiltration. Thus, the mechanical properties of biomimetic scaffolds must be similar to the properties of the replaced bone tissue to prevent stress shielding.

Biomimetic scaffolds for bone regeneration also should have important properties such as stiffness, mechanical resistance, and permeability. Additionally, the scaffold should undergo controlled degradation (Senthebane et al. 2017; Makhni et al. 2016). The degradation rate must be as close as possible to the tissue growth rate to maintain stability and structure at implanted site during the bone tissue regeneration process.

As described, the mechanical properties and degradation of the scaffold depend mainly on the biomaterial properties and the 3D structure, geometry, and porosity of the scaffold. In many cases, biomimetic scaffolds are designed to mimic the biochemistry and/or structure of native bone tissue.

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Here, we discuss the design of biomimetic scaffolds, kinds of biomaterials and methods used to fabricate biomimetic scaffolds, growth factors used with biomimetic scaffold for bone regeneration, mobilization of biological agents into biomimetic scaffolds, and studies on (pre)clinical bone regeneration from biomimetic scaffolds. Then, future prospects for biomimetic scaffolds are discussed.

7.2 Design Considerations for Biomimetic Scaffolds

Biomimetic scaffolds are first evaluated in in vitro environments with various compositions of culture media, mechanical stimuli, temperatures, cells, and cell activity that affect the growth of new bone tissue.

Then, the feasibility of using a biomimetic scaffold is determined by considering the bone regeneration processes occurring in vivo based on gender, age, size and kind of bone defect, mechanical and biochemical stimuli, vascularization, and inflammatory and immunological processes expected during bone regeneration using a scaffold (Mastrogiacomo et al. 2005; Guo et al. 2006).

Thus, the methods to fabricate biomimetic scaffolds must be considered, with several basic factors such as porosity, surface/volume ratio, structure, surface shape, and chemistry of the polymer, and composition, structure, and molecular weight of the biomaterial should be considered (Mondschein et al. 2017; Singh et al. 2014; Chua et al. 2016; Sheikh et al. 2017).

Biomimetic scaffolds must promote cellular growth inside of their structures and must react in a controlled manner in vitro and in the specific implantation site *in vivo*. The processes of bone regeneration are complex, so there are many requirements for the design of biomimetic scaffolds. Some of the most important design considerations are indicated below.

7.2.1 Biomimetics

Biomimetic scaffolds should be prepared by patterning, binding of cytokines and/or ligands, and the sustained release of these molecules (Yin et al. 2017; Park et al. 2017). Biomimetic scaffolds should be produced based on an understanding of cells and tissue morphologies and structures in humans. Biomimetic scaffolds should meet certain design requirements to restore the functions of the regenerated bone tissue and show optimal biochemical and topographical features to allow the infiltration of local or implanted mesenchymal stem cells (MSCs) and other osteoprogenitor cells.

7.2.2 Biocompatibility

Biomimetic scaffolds should be compatible with normal cellular activity, including molecular signaling without eliciting or evoking local or systemic adverse responses in the host. Cytotoxicity, genotoxicity, immunogenicity, mutagenicity, and thrombogenicity in the host should be eliminated, minimized, or controlled before the implantation of a biomimetic scaffold.

7.2.3 Biodegradability

Biomimetic scaffolds should degrade at a rate appropriate for their *in vitro* or *in vivo* environments, preferably at a controlled rate, to create space for the formation of new bone tissue. The degraded materials from biomimetic scaffolds should be biocompatible and must be able to be metabolized and eliminated from the body.

7.2.4 Mechanical Properties

Biomimetic scaffolds should show suitable mechanical strength to meet with mechanical requirements for target bone tissues and should retain their structures to serve a mechanical function after implantation. Mechanical properties such as the elastic modulus, tensile strength, fracture toughness, fatiguability, and elongation percentage should be as close as possible to those of the target bone tissues.

7.3 Techniques to Fabricate Biomimetic Scaffolds

Various manufacturing methods have been used to instill specific properties into biomimetic scaffolds. Generally, conventional methods of solvent casting/particulate leaching, phase inversion/particulate leaching, gas foaming, electrospinning, and injection can be used to prepare biomimetic scaffolds (Barabaschi et al. 2015; Holzwarth and Ma 2011; Bhaskar and Lim 2017). These methods provide biomimetic scaffolds with internal structure, including a pore size between 100 and 1000 microns and porosity up to 90%, but result in a randomly arranged structure and limited permeability. Recently, printed scaffolds with oriented structures have been developed, but their porosity is still difficult to control.

7.4 Biomaterials for Biomimetic Scaffolds

To develop biomimetic scaffolds for use in clinical bone tissue engineering, the biomaterials should be biocompatible, possess appropriate mechanical properties, and have characteristics similar to bone. This section reviews naturally derived biomaterials, synthetic biomaterials, and ceramics and their composites that are currently in use and that have been adapted for the manufacture of biomimetic scaffolds to support biological signaling for bone tissue growth and regeneration.

7.4.1 Naturally Derived Biomaterials

Naturally derived biomaterials are biomaterials produced by living organisms. Naturally derived biomaterials have a number of advantages, including the elicitation of only mild inflammatory responses *in vivo*, excellent biocompatibility, and relative availability and ease of acquisition from natural sources (Aamodt and Grainger 2016; Fan and Guan 2016; Li et al. 2016). Another feature of such biomaterials is that they are eventually degraded into CO_2 and water by microorganisms.

Naturally derived biomaterials exhibit batch-to-batch variations in composition that are strongly dependent on the isolation procedure used and differences in immunogenic and mechanical properties. There are several (pre) clinically applicable naturally derived biomaterials with optimized physical and mechanical properties for ideal performance.

Naturally derived biomaterials such as collagen, chitosan, hyaluronic acid, alginate, and fibrin are inherently biocompatible, showing minimal adverse immunogenicity, and are widely used in the fabrication of biomimetic scaffolds described in following paragraph.

Collagen is the major protein component of the extracellular matrix that is relatively abundant and shows outstanding biocompatibility (Ghazanfari et al. 2016). Even though there are serious concerns about the safety of animal tissue-derived collagen, collagen is the material used most commonly for biomedical applications. Collagen-based biomimetic scaffolds can be fabricated through various methods that determine, for example, 3D shape and the inclusion of hydrogels and nanofibers. However, collagen typically lacks the desired mechanical strength. Thus, the mechanical strength of collagen can be increased by chemical treatment or cross-linking. Collagens, therefore, are some of the most promising biomaterials for the preparation of biomimetic scaffolds.

Chitosan is also an abundant biomaterial derived from the shell-crusts of crustacean animals (Correia et al. 2015). It is obtained by the full or partial deacetylation of chitin by alkaline hydrolysis. Chitosan is a biodegradable, biocompatible, non-antigenic, non-toxic, and biofunctional material. Thus, chitosan has been used to form various scaffolds. Specifically, the cationic amino groups on chitosan chains can interact electrostatically with anionic groups or can be modified or functionalized by chemical or physical methods to increase the mechanical strength of these scaffolds.

Hyaluronic acid (HA) is a naturally derived biomaterial found in most connective tissues of the body, including the skin, cartilage, and vitreous humor (Drury and Mooney 2003). HA can be obtained on a large scale without the risk of transmitting animal-derived pathogens. Because HA serves many physiological functions, including regulation of water in tissues and matrices, HA can be widely used to form scaffolds with structural and space-filling properties. HA is an anionic, non-sulfated glycosaminoglycan polyanion. HA properties are significantly improved by cross-linking. Overall, HA is highly biocompatible with tissues and thus is frequently used as a biomaterial to create biomimetic scaffolds for bone regeneration.

Alginate has also been used to make biocompatible, biodegradable, and hydrophilic biomimetic scaffolds (Lee et al. 2017c). Alginate is an anionic polymer with carboxyl groups, and thus it undergoes simple and reversible gelation through interaction with divalent cations such as Ca^{2+}, Sr^{2+}, and Ba^{2+}. Because of this gelation ability, alginates have been widely used as scaffolds of microbeads and/or hydrogels. Additionally, alginate can mix with other naturally derived biomaterials to increase the integrity and mechanical strength of scaffolds.

Fibrin is composed of two essential components: fibrinogen and purified thrombin (Nanditha et al. 2017). When fibrinogen is mixed with thrombin, these materials polymerize to form long fibrin strands that aggregate in structured fibrin clots. Because fibrin is completely biodegradable and highly angiogenic, fibrin is a promising material for the fabrication of bone biomimetic scaffolds to be used for bone tissue regeneration and wound healing.

Other naturally derived biomaterials that will not be discussed here include proteins, albumin, gelatin, heparin, silk, chondroitin 6-sulfate, and acellular dermis.

7.4.2 Synthetic Biomaterials

In contrast to naturally derived biomaterials, synthetic biomaterials can be obtained that (a) show consistent composition and no batch-to-batch variation; (b) allow large-scale production; (c) can be used to create precise designable geometric forms; (d) can be customized with a wide range of mechanical properties; (e) show predictable mechanical properties; (f) and induce minimal immune responses.

Although the synthetic biomaterial itself or its degradation production can induce inflammatory responses, various synthetic biomaterials such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers poly(DL-lactic acid-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), and others are the materials most widely used to fabricate biomimetic scaffolds for bone tissue regeneration.

PLA, PGA, and PLGA with different ratios of glycolic acid and lactic acid are the synthetic polyesters most widely used for the fabrication of scaffolds. Scaffolds fabricated from PLA, PGA, and PLGA are degraded under normal physiological conditions. The degradation rate depends on several conditions such as the degree of crystallinity and amorphousness, molecular weight, copolymer ratios, and environment at the implantation site.

Although the degradation byproducts can induce tissue inflammation associated with the generation of acidic species, PLA, PGA, and PLGA are commercially available and FDA-approved biomaterials that show promise for the fabrication of biomimetic scaffolds for bone tissue regeneration (Jing et al. 2016; Kim et al. 2015; Lin et al. 2017; Armitage and Oyen 2015).

PCL is another biodegradable biomaterial that is considered soft- and hard-tissue compatible and shows biocompatibility similar to that of PLA, PGA, and PLGA. The degradation rate of PCL is slower than that of PGA, PLA, or PLGA. Thus, PCL is ideally suited for long-term implantation applications. PCL is available in a commercial grade and is an FDA-approved biomaterial. Blending or copolymerization of PCL with PGA and PLA can adjust the degradation rate relative to that of PCL alone. Copolymers of PCL with PGA and PLA can be used to satisfy specific demands for bone tissue growth at the appropriate time scale.

Most synthetic biomaterials, therefore, possess appropriate mechanical and biochemical properties and are suitable for fabrication of bone biomimetic scaffolds with adjustable morphological structures.

7.4.3 Ceramics

Even though most naturally derived biomaterials are highly biocompatible, and PLA, PGA, PLGA, and PCL can easily be formed into scaffolds with controlled mechanical properties and biodegradability, biomaterials alone are limited in their applicability to bone regeneration because of their low osteoinductive capacity.

In contrast, bioceramics exhibit good osteoconductivity, high compressive strength, and good bone integration (Dorozhkin 2010; Smith et al. 2015). Bioceramics consist of inorganic oxides and salts. Thus, biomaterial composites that include bioceramics can be used to fabricate osteoinductive and osteoconductive biomimetic scaffolds. Biomimetic scaffolds fabricated from bioceramic composites can biodegrade and exhibit good mechanical strength and the ability to conform.

Calcium phosphates, the mineral components of bone, are composed of calcium ions (Ca^{2+}), orthophosphates (PO_4^{3-}), metaphosphates, or pyrophosphates ($P_2O_7^{4-}$). The most common calcium phosphate, a central component of bone, is hydroxyapatite (HAp), which has a crystalline structure of $Ca_{10}(PO^4)_6(OH)_2$. HAp shows high bioactivity, biocompatibility, and osteoconductivity (Frezzo and Montclare 2016; Koupaei and Karkhaneh 2016).

HAp can be obtained from natural sources or can be synthetized from calcium carbonate and monoammonium phosphate. HAp exhibits osteoconductive characteristics that facilitate bone regeneration.

Other calcium phosphates include calcium sulfate (CS), calcium carbonate, dicalcium phosphate, octacalcium phosphate, β-tricalcium phosphate (TCP), biphasic calcium phosphate, and β-calcium pyrophosphate. Commercially available calcium phosphates are made into many physical forms such as particles, blocks, and cements. In addition, calcium phosphates can be used in biomaterial composites for bone tissue engineering. These composites can be used to fabricate osteoconductive biomimetic scaffolds.

7.5 Growth Factors for Bone Regeneration Using Biomimetic Scaffolds

Biomimetic scaffolds can be manufactured through patterning and mobilization of growth factors such as ligands, hormones, and cytokines. The use of growth factors with biomimetic scaffolds can trigger biochemical signaling for cellular processes such as growth, proliferation, or differentiation. Several growth factors recruit MSCs, differentiate MSCs into chondrocytes and osteoblasts, and promote the proliferation of osteoblasts and chondrocytes for bone regeneration. The growth factors most commonly used in biomimetic scaffolds for bone tissue engineering are summarized below.

Bone morphogenetic proteins (BMPs) can recruit MSCs, differentiate MSCs into chondrocytes and osteoblasts, and promote osteoblast-mediated matrix mineralization (Bessa et al. 2008). BMPs are the prototypical bone regenerative growth factors. When BMPs are incorporation into scaffolds, they promote the growth of new bone tissue inside of these scaffolds. Thus, BMP is most common used growth factors on biomimetic scaffold.

Transforming growth factors-β (TGFs-β) also cause MSCs to differentiate into chondrocytes and may stimulate the proliferation of MSCs, osteoblasts, and chondrocytes (Dinh et al. 2015). Basic fibroblast growth factors (bFGF) also induce MSCs and promote chondrocytes and osteoblast proliferation (Chim et al. 2013). Platelet-derived growth factors (PDGF) similarly increase the proliferation of chondrocytes and osteoblasts, although bone resorption has been shown to be PDGF concentration-dependent (Sánchez et al. 2017). PDGF exhibits chemotactic and mitogenic action on osteoblasts.

Bone regeneration depends on rapid vascularization into the bone scaffold. Thus, the scaffold can be functionalized by the use of growth factors such as vascular endothelial growth factor (VEGF) or bFGF that have angiogenic properties (Wang et al. 2017). VEGF or bFGF both enhance vessel growth into scaffolds.

7.6 Loading of Growth Factors into Biomimetic Scaffolds

To prepare bone scaffolds as biomimetic environments, growth factors can be immobilized on the scaffold. Non-covalent bonding (physical adsorption) and covalent bonding (chemical adsorption) approaches are both well established and allow the introduction of growth factors into a scaffold (Wang et al. 2017).

Physical adsorption occurs through weak interactions such as hydrogen bonding, van der Waals forces, and hydrophobic bonding. Although the introduction of growth factors into a scaffold is quite simple, the strength of the interactions for physical adsorption is dependent on the chemistry of scaffold biomaterial surfaces. Thus, physical adsorption alone may not sufficiently stabilize the growth factors inside a scaffold. Furthermore, growth factor content and conformation cannot be precisely controlled.

In contrast, chemical adsorption can be used to stably introduce growth factors into a scaffold by chemical cross-linking. The growth factors are anchored directly onto the functional groups of the scaffold surface. However, this method may result in side reactions such as scaffold breakdown or structural change in growth factors.

Both adsorption methods can be used to prepare biomimetic scaffolds. Various strategies such as modifying the local concentration of growth factors in the scaffold must be considered. Growth factors in the scaffold must be stable and active throughout the bone regeneration period. Currently, FDA-approved BMP-loaded scaffolds such as INFUSE® and Op-1® are available for orthopedic applications (Pinel and Pluhar 2012).

7.7 Biomimetic Scaffolds for (Pre) clinical Bone Regeneration

Clinical use of biomimetic scaffolds is currently in an embryonic stage, because most research on biomimetic scaffolds is conducted in animal models. Several preclinical studies have examined biomimetic scaffolds from alginate, chitosan, and synthetic polymers (Table 7.1) (Moeinzadeh and Jabbari 2015; Guo et al. 2006; Chua et al. 2016; Sheikh et al. 2017; Park et al. 2017; Bhaskar and Lim 2017; Koupaei and Karkhaneh 2016; Bessa et al. 2008; Wang et al. 2017; Pinel and Pluhar 2012; Re'em et al. 2012; Chen et al. 2011; Kon et al. 2010; Gervaso et al. 2012; Sartori et al. 2017; Zhang et al. 2013; Gotterbarm et al. 2006; Huh et al. 2017; Islam et al. 2015; Ahn et al. 2009; He et al. 2016; Correia et al. 2012; Fuchs et al. 2009; Mitsak et al. 2011; Jang et al. 2016; Chen et al. 2014; Wang et al. 2016; Wu et al. 2012; Lee et al. 2016; Shao et al. 2006; Erisken et al. 2008; Xu et al. 2015; Huang et al. 2013; Nie et al. 2009; Han et al. 2008; Da et al. 2013; Cui et al. 2011; Gupta et al. 2016; Kwon et al. 2015, 2017; Kemppainen and Hollister 2010; Yao et al. 2017; Foroughi et al. 2012; Wongwitwichot et al. 2010). Preclinical studies describing the use of biomimetic scaffolds and stem cells for bone regeneration are presented in the table. Biomimetic scaffold have been used in basic and preclinical research for the treatment of damaged or diseased bone tissues using various adult stem cells. Even though a number of biomimetic scaffolds are available, research must continue to better understand how bone tissues develop in biomimetic scaffolds and which biomimetic scaffold types should be applied in specific clinical situations.

7.8 Future Challenges and Conclusion

Recently, research has been focused on biomimetic scaffolds that mimic the structure and biochemistry of native environments in a living

Table 7.1 Biomimetic scaffolds for (pre)clinical bone regeneration

Biomaterials	Biomaterials for biomimetic scaffolds	Biomimetic agents	Cells	Models	References
Naturally biomaterials	Alginate	TGF-β1, BMP-4	h-MSCs	Rabbit subchondral defects	Moeinzadeh and Jabbari (2015), Bhaskar and Lim (2017), Bessa et al. (2008), Wang et al. (2017), Pinel and Pluhar (2012) and Re'em et al. (2012)
	Chitosan-gelatin/chitosan-gelatin-HAp	TGF-β1, BMP-2 plasmid	r-BMSCs	Rabbit osteochondral defects	Moeinzadeh and Jabbari (2015), Bhaskar and Lim (2017), Wang et al. (2017) and Chen et al. (2011)
	COL1/COL1-HAp	HAp	–	Sheep osteochondral defects	Kon et al. (2010)
	Collagen/HAp	HAp	–	–	Chua et al. (2016), Sheikh et al. (2017) and Gervaso et al. (2012)
	Collagen/Mg-HAp	Mg-HAp	h-MSCs	Mouse skin incisions	Sartori et al. (2017)
	Collagen/PLA	–	r-BMSCs	Rabbit osteochondral defects	Holzwarth and Ma (2011) and Zhang et al. (2013)
	Collagen/TCP	β-TCP	–	Minipig osteochondral defects	Gotterbarm et al. (2006)
	Gelatin/TCP/SF	α-TCP	MG-63	–	Huh et al. (2017)
	Gelatin/chitosan/TCP/CS	β-TCP/CS	–	–	Islam et al. (2015)
	Hyaluronate-Atelocollagen/TCP-HAp	β-TCP-HAp	–	Rabbit osteochondral defects	Ahn et al. (2009)
	Silk fibroin/cellulose nanowhiskers-chitosan	–	MG-63	–	He et al. (2016)
	Silk fibroin	–	h-ADSCs	–	Correia et al. (2012)
	Silk fibroin	–	h-OECs	–	Fuchs et al. (2009)
Synthetic biomaterials	PCL	–	h-fibroblasts	Mouse backs area	Mitsak et al. (2011)
	PCL	BMP2	h-PLSCs	Nude mouse dorsal area	Park et al. (2017), Bessa et al. (2008), Wang et al. (2017) and Pinel and Pluhar (2012)
	PCL	–	h-DPSCs	Nude mouse dorsal area	Jang et al. (2016)
	PCL/COL1	–	Chondrocytes	Nude mouse dorsal area	Chen et al. (2014)

	PCL/graphene	–	h-ADSCs	–	Wang et al. (2016)
	PCL/MP	MP particular	–	–	Wu et al. (2012)
	PCL/PLGA	HAp	r-BMSCs	–	Sheikh et al. (2017) and Lee et al. (2016)
	PCL/TCP	β-TCP	Rabbit BMSCs	Rabbit osteochondral defects	Koupaei and Karkhaneh (2016) and Shao et al. (2006)
	PCL/TCP	β-TCP nanoparticle	–	–	Erisken et al. (2008)
	PCL/PEG	–	h-iPS	–	Xu et al. (2015)
	PHEMA/HA/TCP, HPMA/HA/TCP	HAp/β-TCP	-	–	Huang et al. (2013)
	PLGA/HAp	BMP-2 plasmid	–	Mouse bone defects	Bhaskar and Lim (2017), Wang et al. (2017) and Nie et al. (2009)
	PLGA/BMSCs	TGF-β3	Rabbit BMSCs	–	Guo et al. (2006), Bhaskar and Lim (2017), Wang et al. (2017) and Han et al. (2008)
	PLGA/β-TCP	β-TCP	Rabbit BMSCs	Rabbit osteochondral defects	Da et al. (2013)
	PLGA/β-TCP	β-TCP	Minipig chondrocytes	Minipig osteochondral defects	Cui et al. (2011)
	PLGA/TCP-HAp	TCP/HAp	r-BMSCs	–	Gupta et al. (2016)
	PLGC/hDPSCs	–	h-DPSCs	Rat cranial defects	Kwon et al. (2015)
	PLLA	β-TCP	MG-63	Rat cranial defects	Kwon et al. (2017)
	Poly(glycerol sebacate)	–	Pig chondrocytes	–	Kemppainen and Hollister (2010)
	PVA/TCP	β-TCP	Chondrocytes, SMSCs	–	Yao et al. (2017)
Ceramic biomaterials	HAp	P3HB	–	–	Foroughi et al. (2012)
	TCP, TCP/HAp	β-TCP, HAp	–	Mouse dorsal area	Wongwitwichot et al. (2010)

ADSC adipose-derived stem cell, *BMSC* bone marrow-derived mesenchymal stem cell, *COL1* collagen type I, *DPSC* dental pulp stem cell, *HPMA* 2-hydroxypropyl methacrylate, *iPS* induced pluripotent stem cells, *MP* magnesium phosphate, *OEC* outgrowth endothelial cell, *PEG* poly(ethylene glycol), *PHEMA* poly(2-hydroxyethyl methacrylate), *PLSC* periodontal ligament stem cell, PVA poly(vinyl alcohol), *P3HB* poly-3-hyroxybutyrate, *SMSC* synovium mesenchymal stem cell

organism. Biomimetic scaffolds must be able to accommodate the incorporation of growth factors needed to promote the desired cellular differentiation and maturation and to support the growth and differentiation of (stem) cells for bone regeneration. An overview of biomaterials for the fabrication of biomimetic scaffolds for bone regeneration has been presented here. A number of materials have been successfully applied in animal models, and there will no doubt be significant crossover for human applications of biomimetic scaffolds for better, safer, and more integrated bone regeneration. The challenges are that biomimetic scaffolds must possess the appropriate mechanical and 3D structural properties to mimic in vivo environments and must address immune reactions and bone regeneration in clinical situations. Our knowledge of clinically relevant technologies for biomimetic scaffolds is now growing exponentially and will require collaborative research among biomaterial, biological, and clinical scientists.

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