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Polymeric Scaffolds for Bone Tissue Engineering

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Abstract—Bone tissue engineering is a rapidly developing area. Engineering bone typically uses an artificial extracellular matrix (scaffold), osteoblasts or cells that can become osteoblasts, and regulating factors that promote cell attachment, differentiation, and mineralized bone formation. Among them, highly porous scaffolds play a critical role in cell seeding, proliferation, and new 3D-tissue formation. A variety of biodegradable polymer materials and scaffolding fabrication techniques for bone tissue engineering have been investigated over the past decade. This article reviews the polymer materials, scaffold design, and fabrication methods for bone tissue engineering. Advantages and limitations of these materials and methods are analyzed. Various architectural parameters of scaffolds important for bone tissue engineering (e.g. porosity, pore size, interconnectivity, and pore-wall microstructures) are discussed. Surface modification of scaffolds is also discussed based on the significant effect of surface chemistry on cells adhesion and function.

Keywords—Bone, Tissue engineering, Biodegradable, Polymer materials, Scaffolds.

INTRODUCTION

Bone tissue engineering offers a promising new approach for bone repair.[50,67,96] Compared to traditional autograft and allograft procedures, bone tissue engineering techniques based on autogenous cell/tissue transplantation would eliminate problems of donor scarcity, supply limitation, and pathogen transfer and immune rejection.[15,61] Therefore, it has become a rapidly expanding research area since the emergence of the concept of tissue engineering.[3,19,29,60]

Engineering bone typically uses an artificial extracellular matrix (or scaffold), osteoblasts or cells that can become osteoblasts, and regulating factors that promote cell recruitment, growth differentiation and mineralized bone tissue formation. Among them, highly porous scaffolds play a critical role in cell seeding, proliferation and new tissue formation in three dimensions (3D).[63,64] The scaffold is a 3D substrate for cells, and serves as a template for tissue regeneration. Ideal scaffolds should be biocompatible, biodegradable, and promote cellular interactions and tissue development, and possess proper mechanical and physical properties.[10,39,105]

A variety of materials have been used for replacement and repair of damaged or traumatized bone tissues.[34,49,57,92] These materials include metals, ceramics, polymers (natural and synthetic) and their combinations. Metals and ceramics have two major disadvantages for tissue engineering applications: they are lack of degradability in a biological environment, and their processability is very limited.[68] In contrast, polymers have great design flexibility because the composition and structure can be tailored to the specific needs. They are therefore attractive candidates. Biodegradability can be imparted into polymers through molecular design. Some polymers contain chemical bonds that undergo hydrolysis upon exposure to the body's aqueous environment, and some others can degrade by cellular or enzymatic pathways. For these reasons, polymeric materials have received considerable attention and are widely studied for bone tissue engineering applications.[13] This review will focus on the selection of polymeric materials, scaffold design, and fabrication techniques. Surface modification of scaffolds is also discussed considering the significant effect of surface chemistry on cells adhesion and function. Many other factors such as cell sources, regulating molecules and their delivery, mechanical stimulation, bioreactor design, *in vitro* and *in vivo* cultivation conditions, animal models, and clinical considerations are also critically important for successfully engineering bone and other mineralized tissues. However they are beyond the scope of this paper and will not be covered here.

POLYMERIC MATERIALS

The scaffolds for bone tissue engineering should be fabricated from a biocompatible polymer, which does not have the potential to elicit an immunological or foreign body reaction. The chosen polymer can degrade at a controlled rate in concert with tissue regeneration. The degradation

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products should not be toxic and must be easily excreted by metabolic pathways. Many types of polymeric materials have been used for bone tissue engineering.[4,34,81] They can be simply categorized as naturally derived materials [e.g. collagen and fibrin) and synthetic polymers (e.g. poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers PLGA]. Naturally derived materials have the potential advantage of biological recognition that may positively support cell adhesion and function. However, they may exhibit immunogenicity and contains pathogenic impurities. There is also less control over their mechanical properties, biodegradability, and batch-to-batch consistency. Many of them are also limited in supply and can therefore be costly. An advantage of synthetic polymers is reproducible large-scale production with controlled properties of strength, degradation rate and microstructure. Therefore, synthetic biodegradable polymers have been widely used as vehicles for cell transplantation and scaffolds for tissue engineering.

Collagen is a fibrous protein, and is a main component of extracellular matrix of mammalian tissues including bone, cartilage, tendon, ligament, skin and so on.[6,27,43,86,98] About 25 types of collagen differing in their chemical composition and molecular structure have been identified so far while type I collagen is known to be the most abundant one of all.[46] Mizuno *et al*. utilized type I collagen as the matrix of bone marrow stromal cells and found bone marrow stromal cells could differentiate into osteoblasts on type I collagen matrix *in vivo*, but type II, III, and V collagen did not possess this property.[74] Their results implied that type I collagen matrix offers a suitable environment for the induction of osteoblastic differentiation *in vitro* and osteogenesis *in vivo*. Caplan's group investigated the possibility of using hyaluronic acid-based polymers as cell carriers for tissue-engineered repair of bone and cartilage.[90] Their results indicated that the hyaluronic acid-based delivery vehicles are superior to porous calcium phosphate ceramic with respect to the amount of cells loaded per unit volume of implant. As mentioned above, there are several concerns over the use of natural polymers as scaffolds for bone tissue engineering. These include their weak mechanical strength to give sufficient structural support and protection for the seeded osteoblasts, and the risks of pathogen transmission and immunorejection associated with natural materials from animal and cadaver sources.

Poly(α-hydroxy acids), including PGA, PLA, and their copolymer PLGA, are the most popular and widely used synthetic polymeric materials in bone tissue engineering.[24,36,42,44,55,65,79] These polymers, having a long history of use as degradable surgical sutures, have gained FDA approval for certain human use and are reasonably biocompatible. The ester bonds in these polymers are hydrolytically labile, and these polymers degrade by nonenzymatic hydrolysis. The degradation products of PGA, PLA and PLGA are nontoxic, natural metabolites, and are eventually eliminated from the body in the form of carbon dioxide and water. The degradation rates of these polymers can be tailored to satisfy the requirements from several weeks to several years by altering the chemical composition (e.g. the LA/GA ratio in the PLGA copolymers), crystallinity, molecular-weight, and molecular weight distribution. Although these polymers have already been widely used in bone tissue engineering research, there are ongoing research efforts in improving the functionality of these polymers to further expand their applications. Other polymers have also been investigated for bone regeneration such as polyanhydrides,[32,41,95] polycarbonates,[16,23] polyphosphazene,[52] polyfumarates,[80,107] and poly(butylenes terephthalate)/poly(ethylene oxide).[20]

Synthetic degradable hydrogels are emerged as a way to deliver cells and serve as injectable scaffolds for tissue engineering. PEG-based hydrogel scaffolds have been developed for bone regeneration by several groups.[12,31,59,73] The nonadhesive hydrogel was modified with adhesive RGD peptide to facilitate cell adhesion and spreading. Increased osteoblast attachment and spreading were observed at high RGD concentrations.[12] Poly(propylene fumarate-co-ethylene glycol) hydrogels with a covalently linked RGD peptides were also developed.[8] The RGD concentration was found to regulate osteoblast migration.[8] Poly(aldehyde guluronate) hydrogel was also used as a hydrogel for bone regeneration.[53] In addition to collagen, other naturally derived polymers such as alginate and their modifications were also used as hydrogels for bone tissue engineering.[2,45,48,88] These hydrogels can be injected into the body in a minimally invasive manner for cell and protein delivery.[21,85] However, a disadvantage of hydrogels for bone tissue engineering application is their low mechanical strength, posing difficulties in handling.

Although various polymeric materials are available and have been investigated for bone tissue engineering, no single biodegradable polymer can meet all the requirements for bone tissue engineering scaffolds. Each polymer material has its own characteristic advantages and disadvantages. On the other hand, composite materials often show an excellent balance between strength and toughness and usually improved characteristics compared to their individual components. As a matter of fact, natural bone matrix is an organic/inorganic composite material of collagen and apatites. From this point of view, composite materials are better choices as bone tissue engineering scaffolds.[35,110,111] It is well established that hydroxyapatite (HAP) mimics the natural bone mineral and has been found to possess good mechanical and osteoconductive properties.[1,82,99] Marra *et al.* incorporated HAP granules into poly(caprolactone) and PLGA blends and revealed the formation of collagen 500 μm into the scaffold.[69] Mikos's group mixed HAP short fibers as a reinforcing material to create porous poly(α-hydroxy ester)/HAP composites.[94] The processing technique involves solvent casting and compression molding followed by particulate leaching. The compressive yield

strength of low porosity composite foams increased with increasing HAP fiber content. However, high porosity composite foams, which are suitable for cell seeding, were not reinforced by the introduction of increasing quantities of HAP short fibers. Laurencin *et al.* blended PLGA and HAP in attempt to improve mechanical properties as well as increase the osteoconductivity of PLGA scaffolds.[5,51] In a 21-day osteoblast culture on the PLGA/HAP composite matrix, the cell attachment, function, and mineral formation showed some promising features of the HAP-containing matrix. However, the porosity of the scaffold was quite low, which might not be ideal for long-term cell survival, proliferation, and tissue formation due to mass transport limitations. Our group developed highly porous biodegradable polymer/apatite composite scaffolds through a thermally induced phase separation technique.[110] Porosity as high as 95% was achieved. The mechanical properties of the composite scaffolds were significantly improved over the pure polymer scaffolds. The compressive modulus reached the same range as trabecular bone. The *in vitro* experiments confirmed that the osteoblast survival and growth were significantly enhanced in the PLLA/HAP composite scaffolds compared to the plain PLLA scaffolds.[67] Bone-specific markers, such as osteocalcin and bone sialoprotein, were expressed more abundantly in the PLLA/HAP composite scaffolds than in the PLLA scaffolds. Furthermore, the new bone tissue formation was significantly enhanced and was quite uniformly distributed throughout the PLLA/HAP composite scaffolds in contrast to only surface layer growth in plain PLLA scaffolds. The results from these groups consistently suggest that the strategy of using composite scaffolds of biodegradable polymers and bone mineral-like inorganic compounds is a viable approach in bone tissue engineering.

SCAFFOLD DESIGN AND FABRICATION

Several requirements should be considered in the design of 3D scaffolds for bone tissue engineering.[28,40,105] First of all, an ideal bone scaffold should have sufficient porosity to accommodate osteoblasts or osteoprogenitor cells, to support cell proliferation and differentiation, and to enhance bone tissue formation. High porosity (such as $\geq$90%) is important for scaffolds for any tissue engineering applications, including bone.[67,97] High interconnectivities between pores are also desirable for uniform cell seeding and distribution, the diffusion of nutrients to and metabolites out from the cell/scaffold constructs. The scaffold should have adequate mechanical stability to provide a suitable environment for new bone tissue formation. The scaffold degradation rate must be tuned to match the rate of new bone tissue regeneration in order to maintain the structural integrity and to provide scaffolding cues for tissue formation. Furthermore, the scaffold should have suitable surface chemistry for bone cells adhesion and function.

A variety of processing technologies have been developed to fabricate porous 3D polymeric scaffolds for bone regeneration. These techniques mainly include solvent casting and particulate leaching, gas foaming, emulsion freeze-drying, electrospinning, rapid prototyping, and thermally induced phase separation.

Solvent-Casting and Particulate Leaching Technique

Solvent casting and particulate leaching is a simple and most commonly used method for fabricating scaffolds for tissue engineering.[64,72] This method involves mixing water-soluble salt (e.g. sodium chloride, sodium citrate) particles into a biodegradable polymer solution. The mixture is then cast into the mold of the desired shape. After the solvent is removed by evaporation or lyophilization, the salt particles are leached out to obtain a porous structure. This method has advantages of simple operation, adequate control of pore size and porosity by salt/polymer ratio and particle size of the added salt. Mikos *et al.* used this method to fabricate biodegradable polymer scaffolds to engineer trabecular bone.[72,93] However, the pore shape is limited to the cubic crystal shape of the salt. The difficulty of removing soluble particles from the interior of a polymer matrix makes it hard to fabricate very thick 3D scaffolds.[76] In fact, most of the porous materials prepared by solvent casting and particulate leaching method are limited to thickness ranging from 0.5 to 2 mm.[56] In addition, their limited interpore connectivity is disadvantageous for uniform cell seeding and tissue growth. Sikavitsas *et al.* broken PLGA/salt composite materials into small pieces and compression molded them into thicker samples and then dissolved the salt to generate needed scaffolds for bone tissue engineering studies in bioreactors. Nonetheless, cell growth and mineralization were limited to the outside of the scaffolds, which was attributed to limited internal nutrient transport conditions by the investigators.[89]

Our group developed a method to create biodegradable polymer scaffolds with spherical pore shape and well-controlled interpore connectivity.[62] Paraffin spheres are chosen as pore-generating materials. The created new scaffolding has a homogeneous foam skeleton (Fig. 1). The control of porosity and the pore size can be achieved by changing the concentration of the polymer solution, the number of the casting steps, and the size of the paraffin spheres. The main advantage of this method is that it can ensure the creation of a totally interconnected pore network in the polymer scaffold, which is critical to uniform cell seeding, tissue ingrowth, and regeneration. In addition, the paraffin sphere assembly can be dissolved in some organic solvents but not water. Therefore, certain water-soluble polymers can be involved in fabricating such scaffolds. However, what is the ideal pore size and interpore connectivity of such scaffolds for bone tissue engineering is yet to be investigated.

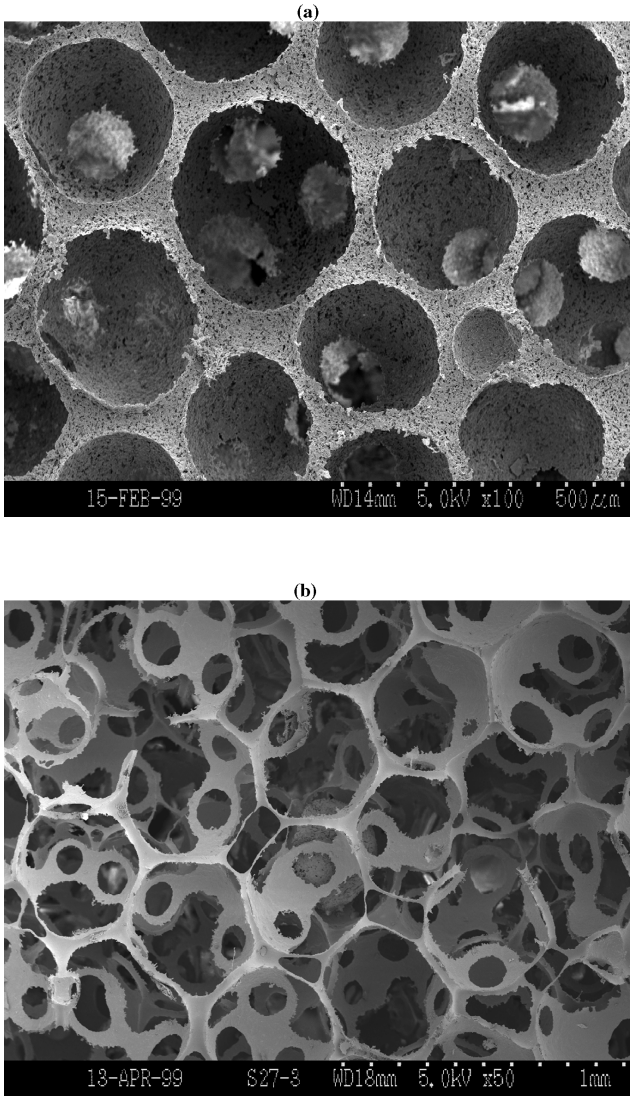

FIGURE 1. SEM micrographs of poly(α-hydroxy acids) scaffolds. (a) PLLA foams prepared with paraffin spheres with a size range of 250–350 μm ($\times$250). (b) PLGA foams prepared with paraffin spheres with a size range of 420–500 μm ($\times$50). (From Ma and Choi,[62] copyright 2000 by Mary Ann Liebert, Inc. Reprinted with permission.)

Gas-Foaming Process

Gas foaming process can be used to fabricate highly porous polymer foams without the use of organic solvents.[18,33,75] In this approach, carbon dioxide (CO_2) is usually used as an agent for the formation of polymer foam. Solid polymer disks are exposed to high pressure CO_2 to allow saturation of CO_2 in the polymer. Thermodynamic instability is then created by rapidly releasing CO_2 gas from the polymer system, followed by the nucleation and growth of gas bubbles in the material. Polymer sponges with a pore size of 100 μm and a porosity up to 93% can be fabricated using this technique. The disadvantage of this method is that it yields mostly a nonporous surface and closed-pore structure, with only 10–30% of interconnected pores.[33,75] The porosity and interpore connectivity can be significantly improved by combining particulate leaching technique with the gas-foaming process although completely eliminating closed pores remains challenging.[33]

Emulsion Freeze Drying

Emulsion freeze-drying technique was used for the fabrication of highly porous PLGA scaffolds.[101,102] The processing method consists of creating an emulsion by homogenization of a polymer solution (in an organic solvent) and water mixture, rapidly cooling the emulsion to lock in the liquid state structure, and removing the solvent and water by freeze-drying. Scaffolds with porosity greater than 90% and a pore size ranging from 20 to 200 μm can be fabricated with this method.[101] One disadvantage of this technique is the closed pore structure in the resulting matrix.[76]

Electrospinning Technique

Electrospinning is a fabrication process that uses an electric field to control the formation and deposition of polymer fibers onto a target substrate.[9,38,70,83,108] In electrospinning, a polymer solution or melt is injected with an electrical potential to create a charge imbalance. At a critical voltage, the charge imbalance begins to overcome the surface tension of the polymer solution to form an electrically charged jet. The jet within the electric field is directed toward the ground target, during which time the solvent evaporates and fibers are formed. This electrospinning technique can fabricate fibrous polymer scaffolds with fiber diameters ranging from several microns down to several hundred nanometers.[54] The 3D scaffold shapes other than sheets or cylinders have not been demonstrated using this technique.

Rapid-Prototyping Techniques

Rapid prototyping is a technology based on the advanced development of computer science and manufacturing industry.[106] The main advantage of these techniques is their ability to produce complex products rapidly from a computer-aided design (CAD) model. One of these rapid prototyping techniques, called 3D printing, was first developed at the Massachusetts Institute of Technology and has been used to process biodegradable polymer scaffolds for tissue engineering applications.[26,84] This process generates components by ink-jet printing a binder on to sequential powder layers. The operation parameters such as the speed, flow rate, and drop position can be computer controlled to produce complex 3D polymer scaffolds. Biological agents, such as growth factors, can also be incorporated into the scaffolds in the printing process. However, the limitation of this method is that the resolution is determined by the jet size, which makes it difficult to design and fabricate scaffolds with fine microstructures. The porosity of the scaffold

fabricated with this method is low, and the mechanical properties of the scaffolds have to be significantly improved.[108]

Thermally Induced Phase Separation

The controlled thermally induced phase separation process was first used for the preparation of porous polymer membranes. This technique was recently utilized to fabricate biodegradable 3D polymer scaffolds.[109] In this approach, the polymer is first dissolved in a solvent at a high temperature, liquid–liquid or solid–liquid phase separation is induced by lowering the solution temperature. Subsequent removal of the solidified solvent-rich phase by sublimation leaves a porous polymer scaffold.[58,76,87,109] The pore morphology of the scaffolds varies depending on the polymer, solvent, concentration of the polymer solution and phase separation temperature. One advantage of this method is that the fabricated scaffolds often have good mechanical properties. For example, a PLLA scaffold fabricated using a solid–liquid phase separation technique has a modulus approximately 20 times higher than that of the scaffold fabricated using the well-documented salt-leaching technique from the same polymer and with the same porosity.[67] However, this method usually generate scaffolds with a pore size of 10–100 μm, which may not be ideal for osteoblastic cell seeding and bone tissue growth. Using a coarsening process in the later stage of thermally induced phase separation, macroporous scaffolds with a pore diameter greater than 100 μm can be generated.[76,100]

By using a solid–liquid phase separation technique, our group fabricated biodegradable polymeric scaffolds with a parallel array of microtubules (Fig. 2).[65] Phase separation was induced using a uniaxial temperature gradient to obtain the oriented microtubular scaffolds. The porosity, diameter of the microtubules, the tubular morphology and their orientation can be controlled by fabrication parameters such as polymer concentration, solvent type, and temperature gradient. The mechanical properties of these scaffolds are also anisotropic, similar to oriented tissues. The new microtubular architecture may serve as superior scaffolds for the engineering of a variety of tissues with fibrillar and tubular architectures.

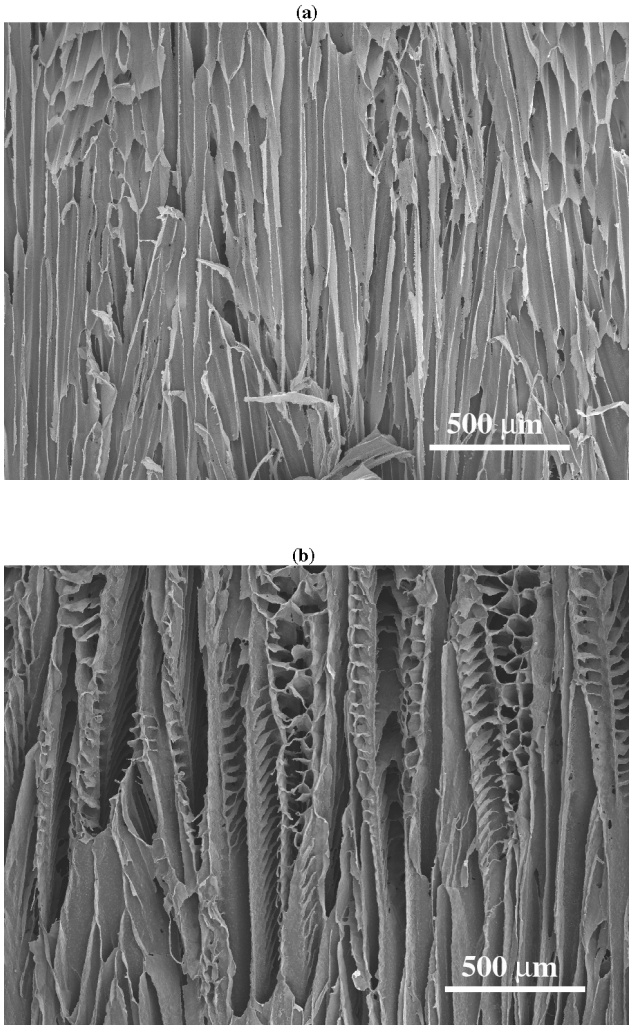

FIGURE 2. SEM micrographs of porous PLLA scaffolds prepared in benzene or dioxane solutions using a phase-separation technique. (a) 2.5% (wt/v) PLLA/benzene, uniaxial temperature gradient, longitudinal section. (b) 5% (wt/v) PLLA/dioxane, uniaxial temperaure gradient, longtitudinal section. (From Ma and Zhang,[65] copyright 2001 by John Wiley & Sons, Inc. Reprinted with permission.)

Collagen is one of the main extracellular matrix components of bone tissue, and its nano-fibrous architecture has long been noticed to play a role in cell adhesion, growth and differentiated function in tissue cultures.[22,30,47,91] To mimic the nanofibrous architecture, our group developed a novel liquid-liquid phase separation technique to create a 3D interconnected fibrous network with a fiber diameter ranging from 50 to 500 nm (Fig. 3).[66] Typically, the nanoscale fibrous matrices were fabricated with five steps: polymer dissolution, phase separation and gelation, solvent extraction, freezing, and then freeze-drying under vacuum. The fiber network formation depends on the gelling temperature and the solvent of the polymer solution. This nanofibrous matrix has a much higher surface-to-volume ratio than those of fibrous nonwoven fabrics fabricated with the textile technology or foams fabricated with other techniques. When combined with the porogen leaching technique, synthetic polymer scaffolds are created with architectural features at several levels, including the anatomical shape (defined by a mold), macroporous elements (100 μm to millimeters), interfiber distance (microns), and the diameter of the fibers (50 to 500 nm).[103,112] These synthetic analogues of natural extracellular matrices combine the advantages of the synthetic biodegradable polymers and the nanoscale architecture similar to the natural extracellular matrix. They were found to selectively enhance protein adsorption and promote osteoblastic cell adhesion.[103]

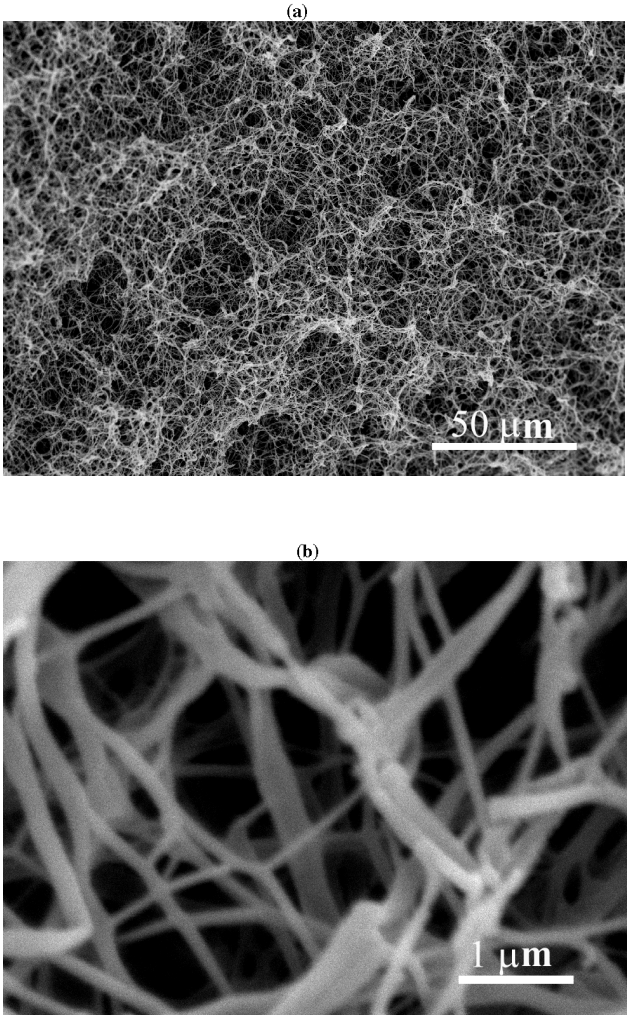

FIGURE 3. SEM micrographs of a PLLA fibrous matrix prepared from 2.5% (wt/v) PLLA/THF solution at a gelation temperature of 8°C: (a) ×50; (b) ×20K. (From Ma and Zhang,[66] copyright 1999 by John Wiley & Sons, Inc. Reprinted with permission.)

Surface Modification

In tissue engineering, it is important to consider the interactions of cells with the scaffolding materials. The nature of the surface can directly affect cellular response, ultimately influencing the rate and quality of new tissue formation. Surface chemistry as well as surface topography determine whether protein molecules can adsorb and how cells attach and align themselves.[11] Although a variety of synthetic biodegradable polymers have been used as tissue engineering scaffolding materials, one disadvantage of these scaffolds is their lack of biological recognition on the material surface. Hydrophobic polymers do not provide the ideal environment for cell-material interactions.[71] Therefore, surface modification of polymeric scaffolds is an active research area.[77,104]

Gao *et al.* described a procedure for surface hydrolysis of PGA scaffold under strong alkaline condition to increase cell seeding density and improve biomaterial-cell interactions.[25] Hydrolysis of ester bonds on the surface of PGA fibers changes the surface properties and results in higher seeding density and more spreading of cells as compared to unmodified PGA scaffolds. Cai *et al.* grafted chitosan on to poly(D,L-lactic acid) (PDLLA) by a coupling reaction on partially hydrolyzed PDLLA surface. The adhesion and proliferation of osteoblasts on modified PDLLA films were improved compared to the control PDLLA films.[14] The limitation of this method is that it is technique sensitive and hydrolysis also alters the surface morphology and bulk mechanical properties.

Langer's group synthesized poly(L-lactic acid-co-L-lysine) and chemically attached RGD peptide to the lysine residue of the copolymer.[7,17] This approach combines the advantage of both natural and synthetic materials. The peptide content of the copolymer and their resulting chemical and physical characteristics could be varied in a controlled fashion by changing the molar ratio of the peptide to lysine units. These poly(α-hydroxy acid)-based copolymers can be further modified by chemical attachment of a variety of biologically active molecules to meet the specific needs of biomedical and tissue engineering applications.

Plasma exposure is an effective procedure for surface etching. Nitschke *et al.* utilized low pressure ammonia plasma treatment for the modification of poly(3-hydroxybutyrate) (PHB) thin films.[78] The introduction of amine function was used for subsequent protein immobilization. The plasma treatment of PHB induced a durable conversion from a hydrophobic into a hydrophilic surface without significantly altering the morphology. Hollinger's group proposed a surface modification method using NH_3 plasma treatment, followed by the attachment of poly(L-lysine) and RGD peptide.[37] The surface-modified polymer films enhanced osteoprogenitor cell attachment. Because of the limited plasma penetration, this method can only be used for two-dimensional (2D) films or very thin 3D structures.

As discussed earlier, most of the surface modification work this far has been focusing on 2D film surfaces or very thin 3D constructs. True 3D scaffolding surface modification is still a challenge. This is an area that has significant needs and potential for growth. Our group developed a biomimetic process that allows the *in situ* apatite formation on the internal surfaces of the pore walls of polymer scaffolds using simulated body fluids (SBF).[111] A large number of microparticles with nano-featured flake- and needle-shaped bone-like apatites was grown on the internal surfaces of the porous polymer scaffolds (Fig. 4). The particle size and their coverage of pore surfaces can be controlled by the incubation conditions such as SBF concentration, incubation time, pH value, pretreatment using aqueous solution and so forth to achieve a desired surface modification pattern. In addition to the aimed surface chemical modification for improved osteoconductivity, the mechanical properties of the scaffolds

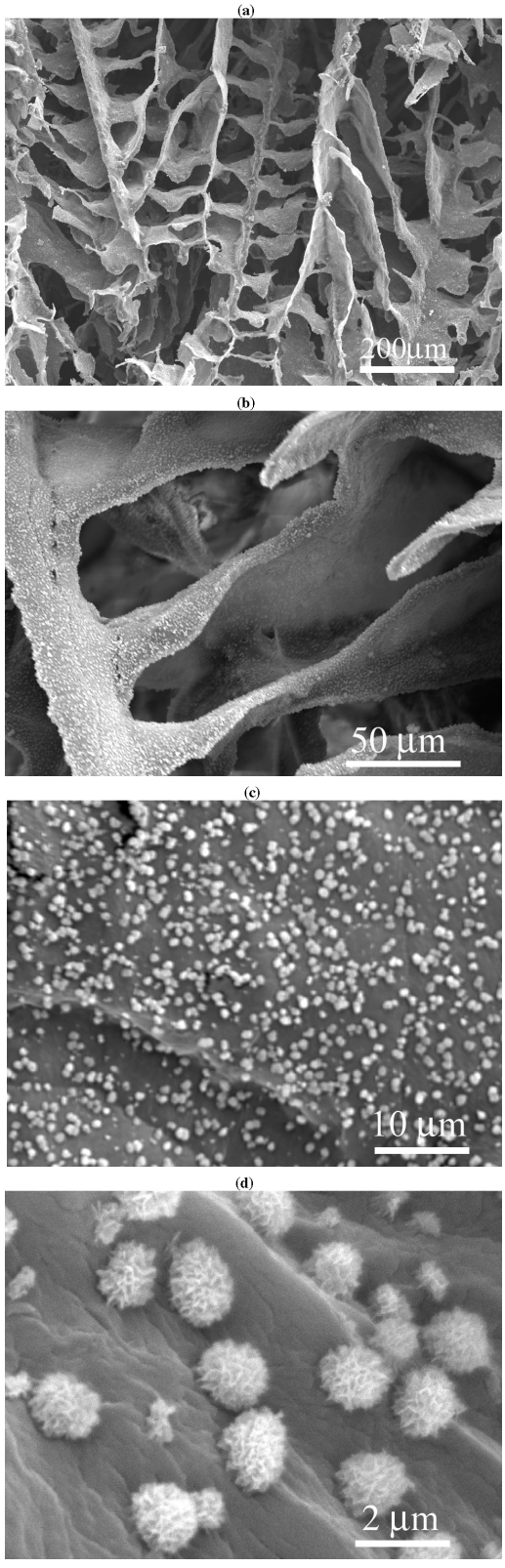

FIGURE 4. SEM micrographs of a PLLA scaffolds incubated in a simulated body fluid for 30 days: original magnifications (a) ×100, (b) ×500, (c) ×2000, and (d) ×10,000. (From Zhang and Ma,[111] copyright 1999 by John Wiley & Sons, Inc. Reprinted with permission.)

were also significantly improved over the plain polymer scaffolds.[111]

PERSPECTIVES

The requirements of scaffolds for bone tissue engineering are complex. A variety of characteristic parameters, such as degradation rate, mechanical strength, porosity, pore size, pore microstructures, surface chemistry, and topography, should be carefully considered and controlled for the design and fabrication of scaffolds to meet the needs of a specific tissue engineering application. Although the ideal matrix materials and 3D scaffolds for bone tissue engineering have yet to be developed, much progress has been made during the last 10 years. The development, fabrication, and analysis of novel biodegradable polymeric biomaterials and scaffolds will still constitute a centerpiece of the research efforts in the field of bone tissue engineering. Using polymer scaffolding to controllably manipulate osteoblastic cell function is still in its infancy and expansion of this field will likely enable development of new therapies and technologies for bone tissue repair and regeneration.

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