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Synthetic biodegradable functional polymers for tissue engineering: a brief review

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Abstract

Scaffolds play a crucial role in tissue engineering. Biodegradable polymers with great processing flexibility are the predominant scaffolding materials. Synthetic biodegradable polymers with well-defined structure and without immunological concerns associated with naturally derived polymers are widely used in tissue engineering. The synthetic biodegradable polymers that are widely used in tissue engineering, including polyesters, polyanhydrides, polyphosphazenes, polyurethane, and poly (glycerol sebacate) are summarized in this article. New developments in conducting polymers, photoresponsive polymers, amino-acid-based polymers, enzymatically degradable polymers, and peptide-activated polymers are also discussed. In addition to chemical functionalization, the scaffold designs that mimic the nano and micro features of the extracellular matrix (ECM) are presented as well, and composite and nanocomposite scaffolds are also reviewed.

Keywords

synthetic biodegradable polymers; functional polymers; scaffolds; tissue engineering

1 Introduction

Accidents and diseases result in tissue losses and organ failures. Organ transplantation became successful in the early 1960s owing to the success of immunologic suppression in the clinical setting [1]. However, transplantation is greatly restricted by the dearth of donor

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organs. Tissue engineering is a new approach to the problem of tissue and organ under-supply. Tissue engineering has been defined as an interdisciplinary field that applies the principles of engineering and the life sciences to the development of biological substitutes that restore, maintain, or improve tissue function [2]. In addition to its therapeutic application, in which the new tissue is either grown inside a patient (*in vivo*) or outside a patient (*in vitro*) and then transplanted, engineered tissue can also be used for diagnostic applications. In these, the tissue is cultured *in vitro* and used for determining drug metabolism and uptake, toxicity, and pathogenicity [3]. In the tissue engineering process, a biodegradable porous scaffold plays a critical role [4]. In addition to providing a tissue template, scaffolds should support cell attachment, proliferation, and differentiation, as well as neo-tissue genesis. Therefore, the chemical composition, physical structure, and biologically functional moieties are all important attributes to scaffolds for tissue engineering [5, 6]. Ideally, a scaffold should: (i) be a biocompatible and biodegradable substrate with tunable degradation rates and nontoxic degradation products; (ii) have a three-dimensional (3D) and highly porous and interconnected pore network, to facilitate nutrient and waste transport; (iii) have mechanical integrity to support regeneration; and (iv) have the appropriate surface chemistry and surface topography to positively interact with cells [7, 8]. Various materials have been developed as scaffolds for tissue engineering, including metals, ceramics, and polymers. Of these materials, polymers possess great processing flexibility and biodegradability that can be endowed through structural design [9]. Therefore, polymers (including natural polymers, natural-polymer-derived materials, synthetic polymers, and synthetic polymers made of natural monomers or modified with natural moieties) are currently the dominant scaffolding materials in tissue engineering [10]. This review is not intended to be a complete review of all the polymers used in tissue engineering. Instead, the focus of this review is on synthetic biodegradable polymers with biological functionality for tissue-engineering applications.

2 Polymers for solid-state porous scaffolds

2.1 Synthetic biodegradable polymers

The extracellular matrix (ECM) consists of a variety of proteins and polysaccharides that are assembled into an organized network that provides structural support to cells. Naturally derived polymers have the potential advantage of supporting cell adhesion and function. Collagen, gelatin, silk, and alginate are commonly used natural polymers for scaffolds [11, 12]. However, concerns over the complex structural composition of natural polymers, as well as immunogenicity and pathogen transmission, have driven the development of synthetic polymers as scaffolding materials. Synthetic polymers usually have controlled structure, a higher degree of processing flexibility, and no immunological concerns [13]. This review summarizes the most frequently used synthetic polymers for tissue-engineering applications.

Aliphatic polyester—These polymers can form stable porous materials that do not dissolve or melt under *in vitro* tissue culture conditions that serve as predesigned 3D scaffolds. Aliphatic polyesters are the most frequently used synthetic biodegradable polymers in tissue regeneration [14]. These polymers usually undergo degradation through

hydrolysis of the ester groups in their backbones; degradation rates and degradation products can be tuned according to composition, structure, and molecular weight [15]. Polylactide (PLA), polyglycolide (PGA), and their copolymer poly(lactide-*co*-glycolide) (PLGA) (Figure 1) are commonly synthesized by a ring-opening polymerization of the monomers (lactide and/or glycolide) [16]. In addition to their biodegradability and biocompatibility, these polymers are among the few synthetic polymers approved by the U.S. Food and Drug Administration (FDA) for human clinical applications such as surgical sutures and some implantable devices. With its many advantageous properties, PGA is one of the most widely used polymers for scaffolds. PGA is highly crystalline due to its chain-structural regularity. It degrades rapidly in aqueous solutions or *in vivo* and loses its mechanical integrity between 2 and 4 weeks, depending on the molecular weight and physical structural of the material and the degradation conditions. PGA was developed into the first synthetic absorbable suture; as one of the most widely used scaffolds in tissue engineering today, it has been fabricated into a wide variety of nonwoven fibrous fabrics [14, 17].

PLA is also widely used as a scaffolding material because of its biodegradability [18]. PLA is more hydrophobic than PGA, due to the extra methyl group in PLA's repeating units. It takes months to years for PLA scaffolds to lose mechanical integrity either *in vitro* or *in vivo*. Our group [19] synthesized a series of biodegradable amphiphilic poly [hydroxyalkyl (meth)acrylate]-graft-poly(L-lactic acid) copolymers that have pendant hydroxyl groups along the copolymer main chains, and show faster degradation rates than the PLLA homopolymer. To obtain intermediate degradation rates between PLA and PGA, PLGAs with varying lactide/glycolide ratios are synthesized.

Poly(ε-caprolactone) (PCL) (Figure 1) is also used in tissue engineering and other biomedical applications [20, 21]. PCL can be degraded by microorganism, hydrolytic, enzymatic, or intracellular mechanisms under physiological conditions. PCL is a semi-crystalline polymer with a very low glass-transition temperature of around −60 °C. Thus, it is always in the rubbery state and has high material permeability under physiological conditions. However, PCL degrades at a much slower rate than PLA, PGA, and PLGA, which makes PCL less attractive for general tissue regeneration applications but more attractive for long-term implants and drug-delivery systems [22, 23].

Polyanhydrides—Polyanhydrides have been synthesized easily from available, low-cost sources and have been manipulated to meet desirable characteristics [24]. Polyanhydrides are biocompatible and degradable *in vivo* into nontoxic diacid byproducts that can be eliminated from the body as metabolites. They were initially designed primarily for drug-delivery applications, because these polymers are very hydrophobic and undergo degradation through surface erosion [25]. Drugs can be well protected when embedded in such polymers because almost no water penetrates before the polymer erodes [26]. They have been explored for tissue engineering scaffolds as well.

Polyphosphazenes—Compared to poly(α-hydroxy acids) and poly(anhydrides), polyphosphazenes (Figure 1) are a relatively newer class of biodegradable polymers [27]. Polyphosphazenes are usually of high molecular weight, and as linear polymers have an inorganic backbone of alternating phosphorous and nitrogen atoms with two side groups

attached to each phosphorous atom (Figure 1). Various synthetic methods have been used to synthesize these polymers, and to achieve different properties for them by changing the pendent groups [28]. Polyphosphazenes have found more and more applications in controlled-release systems and in tissue-engineering research [29, 30]. For example, the carboxylic acids L-alanine and L-phenylalanine have been protected by long aliphatic chains consisting of 5 to 8 carbon atoms, and then the amino groups have been subjected to nucleophilic substitution reactions with poly(dichlorophosphazene) to synthesize biodegradable alanine and phenylalanine alkyl ester [31]. Because these polymers combine the hydrolytic sensitivity of the amino acid ester polyphosphazenes with the elastomeric characteristics induced by the long-chain alkoxy polyphosphazenes, they have potential as scaffolds for soft-tissue regeneration.

Polyurethanes—Polyurethanes (PUs), which remain one of the most popular groups of biomaterials, are used for a broad range of biomedical applications [32]. They are popular because of their segmented-block structural character, which endows them with a broad range of versatility in terms of tunable mechanical properties, physical properties, biological properties, blood and tissue compatibility, and more recently their biodegradability [32]. Due to their toughness, durability, biocompatibility, and improved biostability, PUs have been traditionally used as biostable and inert materials in heart valves, vascular grafts, catheters, and prostheses [33]. In the late 1990s, interest in the design of resorbable/degradable PUs for tissue engineering and drug delivery was high [34]. Biodegradable PUs can be synthesized through the incorporation of hydrolyzeable segments into their backbones [32, 33]. The recent development of amino-acid-derived diisocyanates and biocompatible aliphatic diisocyanates with lower toxicity than traditional diisocyanates such as 4, 4′-methylenediphenyl diisocyanate and toluene diisocyanate, has provided new opportunities to synthesize biocompatible and biodegradable polyurethanes. Another desirable feature of the amino-acid-based polymer systems is their proven ability to promote cell adhesion and proliferation without adverse effects [35].

Poly(glycerol sebacate)—Poly(glycerol sebacate) (PGS) (Figure 1) is a relatively new synthetic polymer; as a biodegradable and biocompatible polymer, it is increasingly used in various biomedical applications [36]. The Langer group first reported tough biodegradable PGS synthesized for soft-tissue engineering in 2002 [37]. The starting materials for the synthesis of PGS are glycerol and sebacic acid. Glycerol has been approved by the FDA for use as a humectant in foods; as the natural metabolic intermediate in ω-oxidation of medium- to long-chain fatty acids, sebacic acid has been proven to be safe *in vivo* [38]. PGS, which is relatively inexpensive to produce, exhibits thermoset elastomeric properties. In addition, PGS can be tuned to achieve mechanical properties and degradation rates targeted to a specific application by controlling curing time, curing temperature, reactant concentrations, and, in acrylated PGS, the degree of acrylation [39]. PGS has mainly been targeted for soft-tissue engineering, such as cardiac muscle, blood, nerve, cartilage, and retina, owning to its elastomeric nature [40–42]. Applications of PGS have been expanded to drug delivery, tissue adhesive, and hard-tissue regeneration as well [40–42].

Polymers for hydrogels—Hydrogels are crosslinked hydrophilic polymers that can absorb large amounts of water without dissolution. Hydrogels are promising candidates for certain tissue engineering applications owing to their structural similarity to soft tissue, allowance of minimally invasive procedures, and excellent biocompatibility [43]. Among the synthetic hydrogels, poly (ethylene glycol) (PEG) is the most extensively studied for tissue-engineering research. PEG has been used as a model polymer to study the effect of adhesion peptides because it has been shown to prevent protein and cell adhesion [44, 45]. Peptide-grafted PEG hydrogels can support dynamic adhesion of endothelial progenitor cells. Peptide-modified PEG materials have been used to study the relationships between cell adhesion and migration, as well as between peptide density and spacing [46]. However, PEG hydrogels are not degradable. One way to impart degradability to PEG is to synthesize diblock, triblock, and multiblock copolymers of PL(G)A/PEG via ring-opening polymerization of lactide and/or glycolide in the presence of PEG and catalysts [47, 48]. Another way is to introduce enzyme-degradable linkages into the PEG backbone [49, 50].

2.2 Functional synthetic biodegradable polymers

The polymers discussed above are the most widely used degradable materials in tissue engineering. However, these polymers usually lack sites from which to interact with cells. Therefore, functional synthetic biodegradable polymers have been developed as scaffolding materials for tissue regeneration.

Conducting polymers—Conducting polymers have electrical and optical properties similar to those of metals and inorganic semiconductors, but they also show attractive properties similar to those of common polymers, such as ease synthesis and good processability [51]. During the 1990s, CPs were found to be able to modulate cellular activities such as cell adhesion, proliferation, and differentiation via electrical stimuli [52–54], which indicate that conducting polymers have great potential applications in tissue engineering (because the regulation of cellular behaviour is crucial for tissue regeneration). Many of these studies were carried out on nerve, bone, muscle, and cardiac cells, as well as mesenchymal stem cells, because these tissues or cells are quite sensitive to electrical stimulation [54]. However, conducting polymers are brittle and not soluble in common organic solvents. Therefore, polymer blends and composites that are composed of conducting polymers such as polypyrrole (PPy) and polyaniline (PANi), and biodegradable polymers including synthetic and natural polymers, have been developed and extensively investigated [3]. For example, a novel electrically conductive biodegradable composite material based on PPy nanoparticles and poly(D,L-lactide) (PDLLA) was prepared by emulsion polymerization of pyrrole in a PDLLA solution, followed by precipitation [55]. The conductivity of the composite increased by six orders of magnitude with the PPy content increasing from 1% to 17% in the blends. The growth of fibroblasts cultured on the composite films was up-regulated under stimulation by direct current.

In another example, conductive meshes were prepared by coating PPy on random or aligned electrospun PLGA nanofibers by chemical polymerization of pyrrole [56]. PPy-PLGA electrospun meshes supported the growth and differentiation of rat pheochromocytoma 12 (PC12) cells comparably to non-coated PLGA control meshes, which indicates that the

composite matrix is suitable as conductive nanofibers for neuronal tissue scaffolds. PC12 cells, stimulated with a potential of 10 mV/cm on PPy-PLGA scaffolds, exhibited 40%–50% longer neurites and 40%–90% more neurite formation than unstimulated cells on the same scaffolds. Furthermore, electrical stimulation of cells on aligned PPy-PLGA fibers led to longer neurites and more neurite-bearing cells than stimulation on random PPy-PLGA fibers (Figure 2). All of these results indicate that a combined effect of electrical stimulation and topographical guidance increases the potential use of these conductive nanofibrous scaffolds for neural tissue applications. Recently, it was demonstrated that a conduit made of a poly (D,L-lactic acid) (PDLLA)/PPy blend could restore a sciatic nerve defect similarly to an autologous nerve graft [57].

Conducting materials that are elastic allow more realistic mimicry of the mechanical properties of ECM, such as skin cells, skeletal muscle, and blood vessels. Elastic electrically conductive scaffolds were prepared by electrospinning a composite of PANi with poly(L-lactide-*co*-ε-caprolactone) (PLCL, Figure 1) [58]. The cell adhesion of human dermal fibroblasts, NIH-3T3 fibroblasts, and C2C12 myoblasts were significantly stronger on the PANi/PLCL nanofibers than on the pure PLCL nanofibers. Moreover, the growth of NIH-3T3 fibroblasts was enhanced under the stimulation of various direct current flows.

Although there are only small amounts of PANi or PPy in the blends or composites of the above systems, the PANi or PPy components are expected to stay *in vivo* as a consequence of applying these materials, because of their non-degradability or poor degradability. However, retaining conducting polymers in the human body for a long time may induce chronic inflammation. Therefore, degradable conducting polymers are highly desirable [3]. Aniline oligomers have well-defined structures, biocompatibility, good solubility in common organic solvents, and electroactivity similar to that of polyaniline [59, 60]. In addition, the oligomers of polyaniline would be consumed by macrophages and subsequently cleared by the kidneys. Therefore, synthesis of degradable and conducting polymers based on aniline oligomers has recently gained more attention [3]. A multiblock copolymer based on polylactide and aniline pentamer was synthesized with the condensation polymerization of hydroxyl-capped PLA and carboxyl-capped aniline pentamer [61]. This copolymer was nontoxic, biocompatible, and helpful for rat C6 cells' adhesion and proliferation. Furthermore, the copolymer was shown to accelerate the differentiation of rat PC-12 cells upon stimulation by electrical signals.

Architecture plays an important role in the performance of polymers. To be able to achieve the optimal mechanical, degradation, thermal and biological properties for a particular biomedical application, architectural diversity is needed [62]. By combining the electroactivity of conducting polymers and the degradability of aliphatic polyesters, we have designed and synthesized a series of linear [63–65], star-shaped [63], hyperbranched [66], and crosslinked [67–69] degradable and electrically conducting polymers and hydrogels based on PLA, PCL, and aniline oligomers (Figure 3). These polymers and hydrogels have good electroactivity. The conductivities of the polymers and hydrogels between 10^{-4} and 10^{-7} S/cm are tuned by the content of the aniline oligomers and the macromolecular architecture [66]. We also found that the hydrophilicity of the polymers was greatly increased after we doped the aniline oligomers with acid. The water-contact angle can be

tuned in the range of 30°–70°, which overcomes the hydrophobicity of the PLA and PCL [70]. The hydrophilic polymers can form hydrogels with an adjustable swelling ratio covering a wide range that is controlled by the degree of crosslinking, the oligoaniline content, and the pH of the surrounding solution. We also developed a method for the facile synthesis of degradable conducting polymers and hydrogels that avoids the multi-step reaction used in the earlier work [64, 65]. Electroactive degradable nontoxic porous tubular scaffolds were also fabricated from a polymer blend of hyperbranched degradable conductive copolymer and PCL, using a modified solution-casting/particle-leaching technique [71]. The conductivity of the films was tuned by adjusting the ratio of hyper-branched degradable conducting copolymer to PCL. The cytotoxicity test with HaCaT keratinocytes indicated that the materials were nontoxic. These degradable electroactive copolymers and hydrogels, with different architectures and properties, have a great potential for meeting the requirements of tissue-engineering applications.

Photo-responsive polymers—Light is a mild stimulus that can be used in the clinic. Therefore, design and synthesis of photosensitive polymers has drawn great interest in recent years. The most frequently studied photochromic groups are azide groups, cinnamoyl groups, and spiropyran, coumarin, and 2-nitrobenzyl groups [72, 73]. Photosensitive properties can be to trigger conformational change of polypeptides. Reversible photoresponsiveness can also be used to change the wettability by surface modification [74]. Light-responsive polymers are applicable in delivery systems during tissue regeneration [75, 76]. For example, employing the inclusion complex of trans azobenzene (AB) and cyclodextrin (CD) as a photoswitchable crosslinker, a light-responsive hydrogel system consisting of AB-functionalized dextran (AB-Dex) and CD functionalized dextran (CD-Dex) have been synthesized as release systems for proteins (Figure 4) [76]. AB-Dex underwent isomerization from *trans* to *cis* upon UV-light irradiation and trans isomers formed an inclusion complex with CD more firmly than *cis* isomers did. Upon UV-light irradiation, trans-AB moieties were changed to *cis* configurations that led to the dissociation of the network by converting the hydrogel into a sol. Using this photoresponsive supramolecular interaction as a molecular switch, the controlled release of proteins can be constructed.

Amino-acid-based polymers—Proteins, which are the major structural components of many human tissues, are essentially amino-acid polymers arranged in a 3D folded structure [77]. Amino-acid-based biomaterials have been known to undergo naturally controlled degradation processes. Synthetic polypeptides have emerged as a type of attractive functional biomaterial because of their unique physical, chemical, and biological properties; they are promising candidates for sutures, haemostatic agents, and scaffolds for tissue engineering [78]. Early studies on the biomedical use of synthetic polypeptides were related to poly(L-lysine) and poly(L-aspartic acid) that were easily prepared, and water-soluble homopolypeptides. These polymers are highly charged in neutral aqueous solution and are the most easily available water-soluble protein mimics. However, they show limited functionality and their polyelectrolyte structure can be problematic because of precipitation with other charged polymers that are present in bodily fluids. (Co)polypeptides of controlled dimensions such as molecular weight and distribution, sequence, and composition can now

be synthesized from polymerization of α-amino acid-*N*-carboxyanhydrides; in addition, polypeptide hydrogels have been developed for tissue engineering applications [79].

Cell-interactive polymers—Biodegradability is generally required for the biomaterials used as scaffolds in tissue engineering, and their degradation rate should match the rate of neo-tissue formation. Enzymatic degradability is one way to render materials degradable [4]. The structure of the degradable sequences should match the active site of respective enzyme(s). Oligopeptide sequences are frequently used as degradable cross-linkers in hydrogels [80]. For example, hydrogels containing oligopeptide crosslinks that are susceptible to chymotrypsin-catalyzed hydrolysis were prepared by *N*-(2-hydroxypropyl)methacrylamide that contained reactive side-chains (*p*-nitrophenoxy groups) with oligopeptide-containing diamines [80]. The degradability of the hydrogels was controlled by the length and detailed structure of the oligopeptide sequence and the crosslinking density.

Poly(ethylene glycol) (PEG) is a hydrophilic polymer that has been used in several clinical applications [81]. PEG-based biomaterials exhibiting degradation by specific enzymes (matrix metalloproteases, aka MMPs) were synthesized [82]. This approach mimics the enzymatic biodegradability of collagen and other natural ECM components. These materials are usually BAB block copolymers of PEG and oligopeptides. The block copolymers terminated with reactive groups are crosslinked to form hydrogel networks, and can be specifically degraded by cell-secreted MMPs (such as collagenase). Enzymatically degradable PEG-based peptide-containing hydrogels were synthesized by the click reaction of 4-arm azido-terminated PEG and two alkyne-terminated peptides: [alkyne]-GFLGK-[alkyne] and ([alkyne]-GFLG)2K (Figure 5). The hydrogels were highly elastic and enzymatic degradation by papain were dependent on the molecular weight of PEG, not peptide [49].

The development of an artificial matrix is critical as both a substrate to control cell behavior and as a tool for examining the roles of cellular microenvironments in biology. Adhesion ligands covalently coupled to hydrogel carriers would allow the control of pre-osteoblast cell attachment, proliferation, and differentiation. Jun *et al*. [83] prepared cell-interactive hydrogels containing an Arg-Gly-Asp (RGD) peptide, cross-linked via bio-inspired enzymatic processes using H_2O_2 in PBS with tetronic-tyramine (Tet-TA) and horseradish peroxidase (HRP) as the initiators (Figure 6). They found that the cell-interactive hydrogels modulated the adhesion and proliferation of myoblasts, depending on the peptide density. In addition, the expression of focal adhesion proteins and myogenic differentiation were dramatically up-regulated in myoblasts cultured on peptide-incorporated hydrogels.

3 Nano and microstructural design in 3D scaffolds

3.1 Nanofibrous scaffolds

In addition to chemical structures, the nano and micro features also play important roles in a tissue-engineering scaffold. Many extracellular proteins possess a fibrous structure with diameters on the nanometer or sub-micrometer scales [84, 85]. For example, collagen (the most abundant ECM protein in the human body) exhibits a fibrous structure with fiber

diameter between 50 and 500 nm [4, 86]. As a temporary extracellular matrix (ECM) for regenerative cells, the scaffold should mimic the nanofibrous features of the natural ECM [87, 88]. We developed a thermally induced phase-separation technique to fabricate 3D nanofibrous PLLA scaffolds [89, 90]. This technique can also be modified to generate 3D nanofibrous gelatin (NF-gelatin) scaffolds to mimic both the physical architecture and the chemical composition of natural collagen (Figure 7) [91]. The obtained NF-gelatin scaffolds have high surface areas, high porosities, well-connected macropores, and nanofibrous pore-wall structures. Compared with commercial gelatin foam (Gelfoam®), the NF-gelatin scaffolds have shown significantly better dimensional stability in a tissue culture environment, which is important for a tissue-engineering scaffold.

3.2 Injectable nanofibrous scaffolds

Irregularly shaped defects and wounds often need to be filled and repaired in clinics. Therefore, injectable scaffolds are advantageous because they allow for easy manipulation with minimally invasive procedures by surgeons, and can fit any defect size or shape [93, 94]. Our group [92] prepared star-shaped poly(L-lactic acid) (SS-PLLA) and fabricated these polymers into injectable nanofibrous hollow microspheres by self-assembly (Figure 8). These nanofibrous hollow microspheres, which possess ECM-mimicking architecture with a highly porous injectable form, have been shown to efficiently accommodate cells and improve cartilage regeneration in comparison with control microspheres. In a critical-size rabbit osteochondral defect-repair model, the nanofibrous hollow microspheres/chondrocytes group showed substantially better cartilage repair than various control groups, which indicates that the nanofibrous hollow microspheres are an excellent injectable cell carrier for cartilage repair.

3.3 Nanocomposite scaffolds

Single-component scaffolds have been widely used in tissue engineering. However, one polymer usually does not meet all the requirements for many tissue regeneration applications. Bone matrix is an organic/inorganic composite material consisting of collagen and apatite. Biomimetic composite scaffolds with an apatite component have been developed for bone tissue engineering [95, 96]. Hydroxyapatite (HAP) ($Ca_{10}(PO_4)_6(OH)_2$) is most frequently used because it closely resembles the natural minerals in bone, but calcium phosphate (CaP) variants and bioglass are also employed due to their biocompatibility [97, 98]. For example, PLGA/HAP composite scaffolds have been fabricated by coating HAP onto PLGA scaffolds using various techniques [99, 100]. We found that HAP in composite scaffolds greatly enhances protein adsorption capacity, suppresses apoptotic cell death, and provides a more favorable microenvironment for bone regeneration [2]. In addition to mimicking the inorganic-organic nature of the natural bone, nano-HAP-polymer composite scaffolds have been developed to mimic the nanosized features of natural-bone mineral [101–103]. Similarly, other inorganic components have been used to make organic and inorganic composite scaffolds. For example, Lei et al. [104] developed nanofibrous gelatin-silica hybrid scaffolds using the thermally induced phase-separation (TIPS) technique.

Mineralized nanofibrous scaffolds have been proposed as promising scaffolds for bone regeneration, due to their ability to mimic both nanoscale architecture and chemical composition of natural bone extracellular matrix. Macroporous, nanofibrous scaffolds were fabricated for bonelike apatite deposition via incubation in a simulated body fluid (SBF) with ion concentrations and pH similar to that of human blood plasma [88, 105]. It was found that calcium phosphates can be deposited directly on the polymer surface, and a uniform and dense layer of nano-apatite was even formed to cover the entire internal pore wall surfaces without clogging the macropores after incubation in an SBF for a reasonable time [88].

An electrodeposition process was recently developed to reduce the mineralization time to less than 1 h [106]. Our group [107] recently compared a novel electrodeposition method with the extensively explored SBF incubation method in terms of the deposition rate, chemical composition, and morphology of calcium phosphate formed on electrospun PLLA fibrous thin matrices. Electrodeposition was two to three orders of magnitude faster than the SBF method in mineralizing the fibrous matrices, which reduced the mineralization time from 2 weeks to 1 h to achieve the same amounts of mineralization (Figure 9). The increase of fiber diameter resulted in a faster mineralization rate for the electrodeposition method but a slower mineralization rate for the SBF incubation method. The chemical composition and morphology of the calcium phosphate can be controlled by varying the electric deposition potential and electrolyte temperature to tune the mixture of dicalcium phosphate dihydrate and HAP with the electrodeposition method. With the SBF method, one can only obtain a low-crystallinity HAP. Compared to neat PLLA matrices, the mineralized electrospun PLLA fibrous scaffolds obtained by either method similarly enhance the proliferation and osteogenic differentiation of preosteoblastic MC3T3-E1 cells.

4 Conclusions

Significant advances in synthetic chemistry are facilitating the development of novel functional polymer materials to control cell behavior at the molecular level. Rapidly advancing nanoscience and nanotechnology enable biomaterials scientists to design functional scaffolds by mimicking the ECM at the nanometer scale to regulate cells and to facilitate tissue regeneration. These functionalized 3D scaffolds are no longer just physical templates for cell growth and tissue formation; they also provide chemical, biomolecular, mechanical, and geometrical signals to cells. These exciting new biomaterials are substantially advancing the filed of tissue engineering.

Acknowledgments

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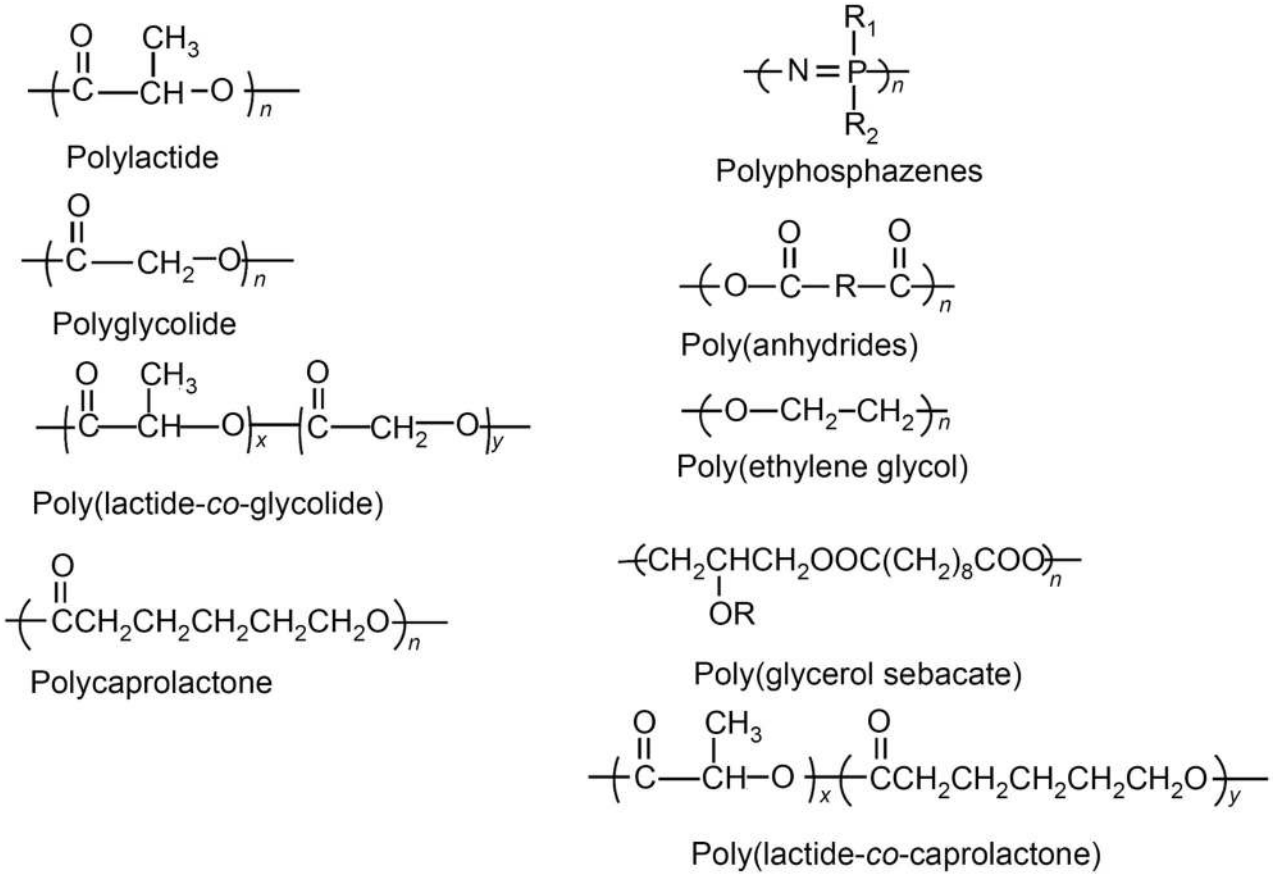

Figure 1.
Polymers frequently used as scaffolds for tissue regeneration.

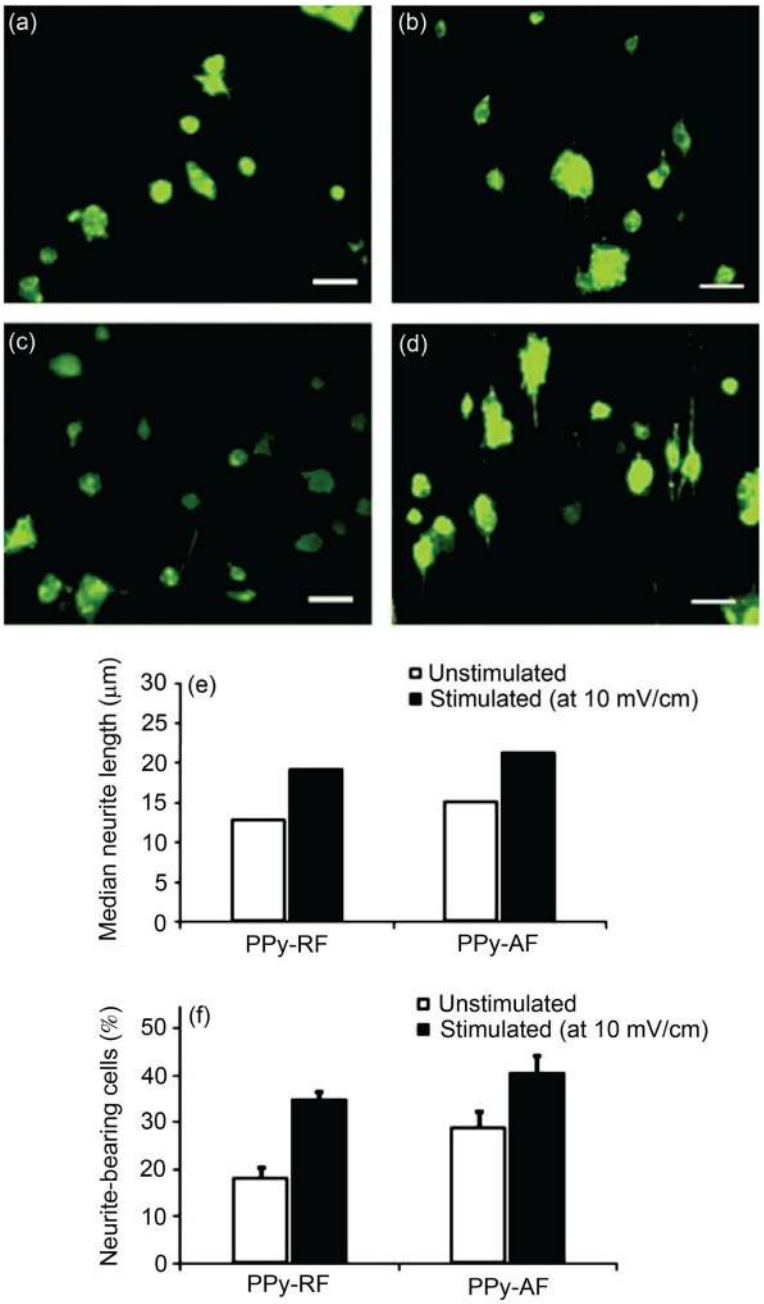

Figure 2.

Representative fluorescence images of electrically stimulated PC-12 cells: (a) polypyrrole-PLGA random fibers (RF) at 0 mV/cm (unstimulated); (b) polypyrrole-PLGA aligned fibers (AF) at 0 mV/cm; (c) polypyrrole-PLGA random fibers at 10 mV/cm; (d) polypyrrole-PLGA aligned fibers at 10 mV/cm. Scale bars are 50 μm. (e) Median neurite lengths and (f) percentages of neurite-bearing PC12 cells when unstimulated and when electrically stimulated (10 mV/cm) on random and aligned polypyrrole-PLGA fibers [56]. Reprinted with the permission of Elsevier.

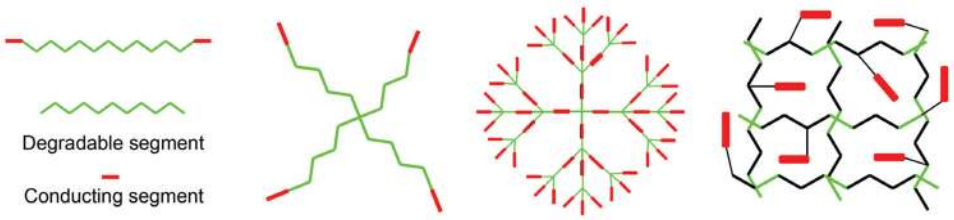

Figure 3.
Degradable conducting polymers with different architectures.

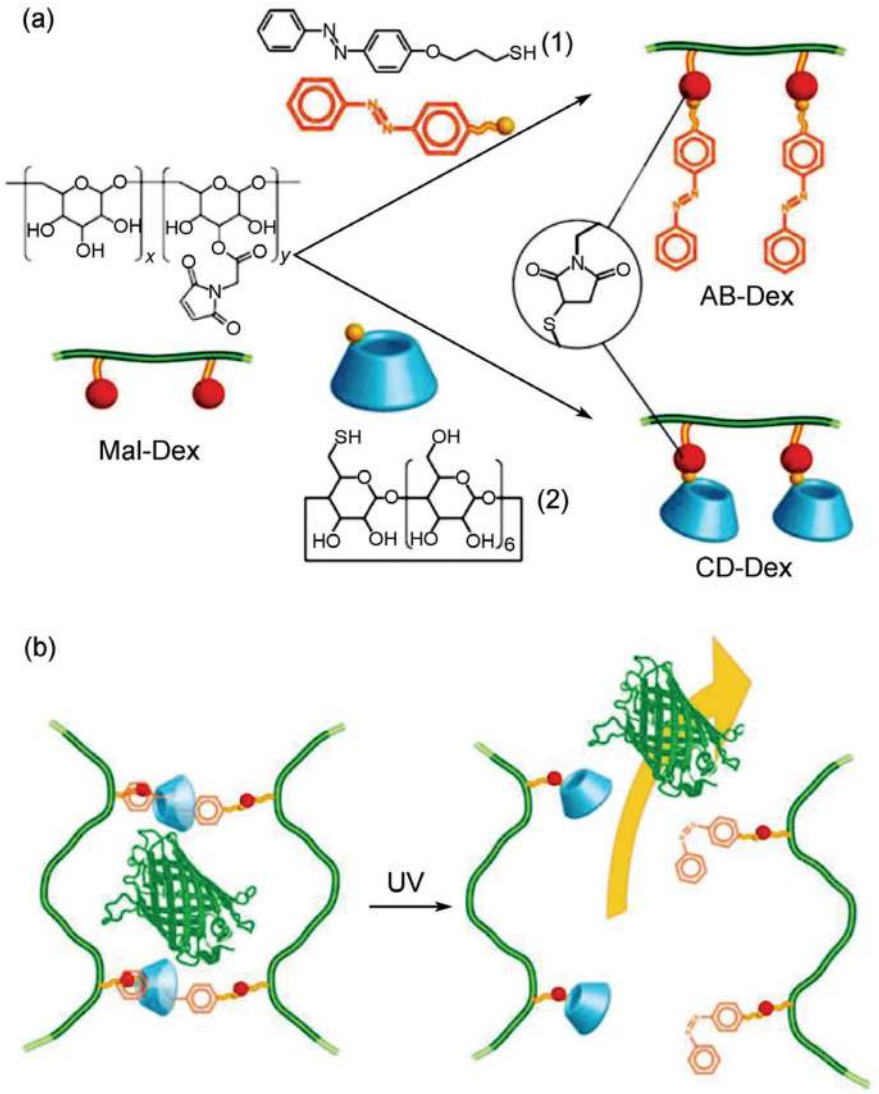

Figure 4.

(a) Synthesis of azobenzene modified dextran (AB-Dex) and cyclodextrin modified dextran (CD-Dex) through the thiol-maleimide reaction. (b) Schematic representation of photoresponsive protein release system. Upon the UV-light irradiation, azobenzene moieties isomerise from *trans* to *cis* configurations that leads to the dissociation of crosslinking points and allows the entrapped protein to be released. Reproduced from ref. [76] with the permission of the Royal Society of Chemistry, 2010.

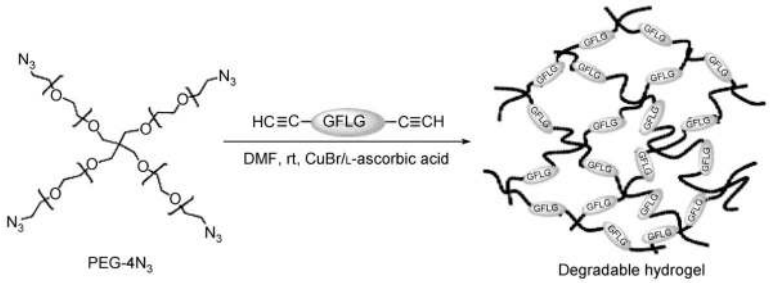

Figure 5.

Synthesis of degradable hydrogels by click reaction of 4-arm PEG-N3 with dialkyne modified peptide [49]. Reprinted with the permission of John Wiley and Sons.

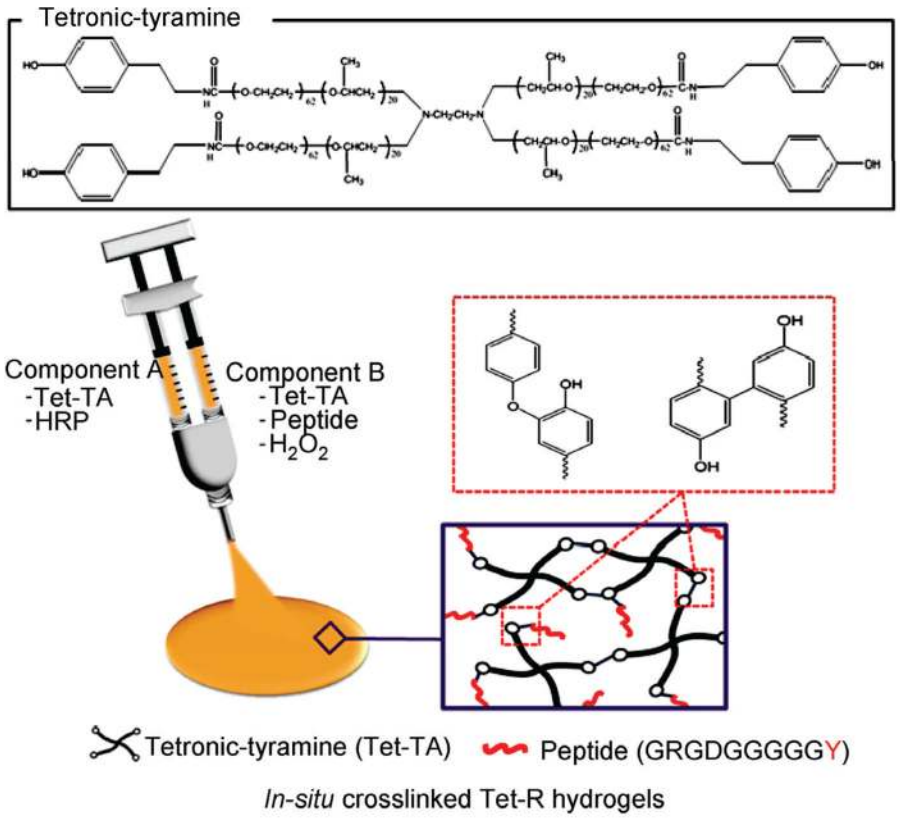

Figure 6.
Formation of peptide-incorporated hydrogels using HRP and H_2O_2 [83]. Reprinted with the permission of Springer Verlag.

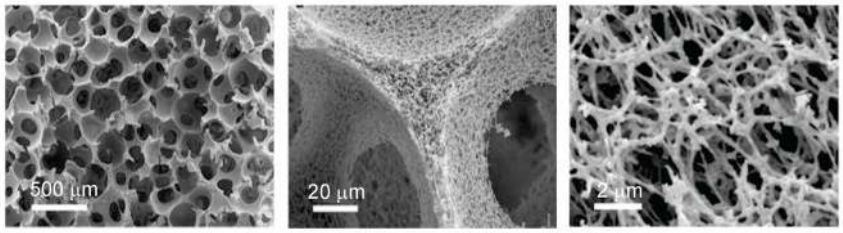

Figure 7.
SEM micrographs of nanofibrous-gelatin scaffold, × 50 (left); pore-wall morphology of nanofibrous-gelatin scaffold, × l000 (middle); high magnification of nanofibrous-gelatin scaffold, × 10000 (right) [91]. Reprinted with the permission of Elsevier.

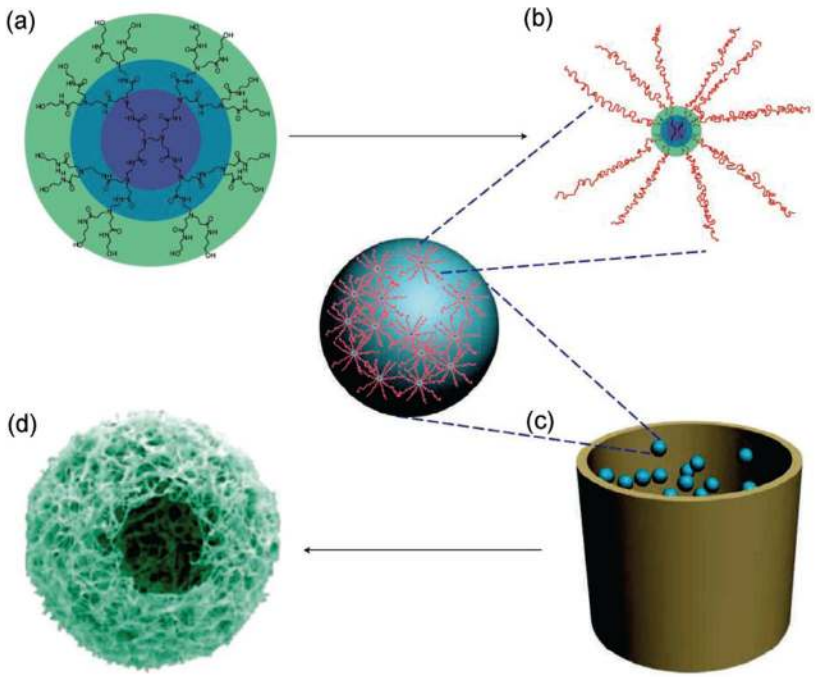

Figure 8.

A schematic synthesis of star-shaped-PLLA and the fabrication of nanofibrous hollow microspheres. (a) PAMAM (G2) as an initiator to synthesize star-shaped-PLLA; (b) the synthesis of star-shaped-PLLA. Red coils represent the PLLA chains. (c) Fabrication of SS-PLLA microspheres using a surfactant-free emulsification process. (d) Nanofibrous hollow microspheres were prepared via phase separation, solvent extraction and freeze-drying [92]. With the permission of Nature Publishing Group.

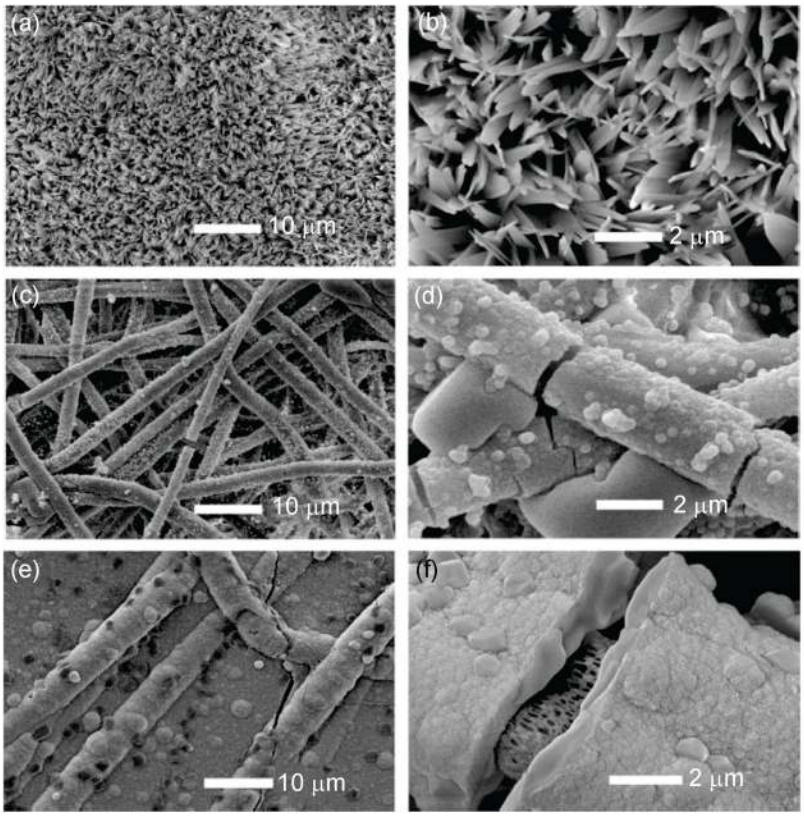

Figure 9.

SEM micrographs of mineralized PLLA matrices. (a) Electrodeposition at 3 V, 60 °C for 60 min, (b) the magnified image of (a) and (c) mineralized in 1.5 × SBF for 12 days, (d) the magnified image of (c) and (e) mineralized in 1.5 × SBF for 30 days, (f) the magnified image of (e) [107]. Reprinted with the permission of Elsevier.