Development of Biological Functions for Polymeric Materials Utilized in Biomedical Application

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The development of biological functions for biomaterials utilized in medical application has been presented on the basis of biocompatibility and biodegradability. It has been found that the biological functions of biomedical polymers are closely correlated to the role of cell functions in the living body. The present paper includes the biodegradable functional polymers synthesized from Krebs cycle acid derivatives and the other polymers such as biological DNA and RNA matrix systems developed for tissue engineering and biomedical applications. The biodegradable copolymer systems containing biological functions are also proposed as more useful biomaterials for biomedical application on the basis of biological adaptability.

Key words: Biomaterials, biological functions, biocompatibility, DNA, RNA, biomedical application

Introduction

The functional polymeric materials obtained from natural resources and living cells are particularly useful for biomaterials utilized in tissue engineering and biomedical applications. Biodegradable functional polymers have been reported to apply to gene carriers and drug delivery systems for medical applications.¹⁻⁵ Some biodegradable polymers have been developed for the purpose of reconstructive generation and targeting drug delivery systems for the biomedical applications.⁶⁻⁸ The medical applications of biodegradable polymers include the absorbable bone plates and other surgical fixation devices, artificial skin substitutes, and carrier systems for the controlled release of drugs in vivo and in vitro systems.⁹⁻¹² The biodegradable polymers have been also used in the development of polymeric matrix for the controlled and sustained release of low molecular-weight therapeutic agents and short-term implants such as suture and surgical staple for medical applications.¹³⁻¹⁵ Such implants should be maintained their chemical and mechanical stabilities in vivo over a sufficient period of time for the fulfillment allowing regeneration of the substituted organ during healing in the living body.¹⁶,¹⁷ The reasons introducing the biological functions into polymeric biomaterials involve bio-adaptability and biodegradation to be improved. The first is that the biodegraded products in the living body should be adapted non-toxically and metabolically from the body, resulting in no need after use as biomaterials. The second one is that the biodegradation may be affected to the controlled drug releasing profiles using polymeric materials as biomaterials in the body. The behaviors of polymeric matrix are contributed to an important role in determining the drug controlled release profile for the living body.

Polymeric Materials Containing Biological Functions

The important polymeric materials containing biological functions are belong to mostly biodegradable natural and synthetic biocompatible polymers such as proteins, poly(α-amino acid), polysaccharides, celluloses, chitosans, poly(anhydrides), poly(esters), poly(ortho esters), poly(phosphazenes), poly(alkyl cyanoacrylates) among the polymeric systems. The useful biomedical polymers in this field should be biodegraded into nontoxic intermediate degraded monomers in the living body. The biodegradation rates of the polymeric materials are also very important in the practical application of biodegradable polymers as biomaterials.

The biodegradation processes of biodegradable polymers should be examined both in vitro and in vivo examinations. The in vitro biodegradation tests can be carried out in pseudo extra cellular fluid, plasma solution, and enzymes buffer solutions. The in vivo biodegradation tests can be usually carried out by
introducing the adjustably degradable biomaterials into the particular site of the living body such as sub-dermal muscle peritoneal cavity, subcutaneous tissue and blood tubes. There are many factors affecting the biodegradability of polymeric materials for biomaterials. They are correlated to primary structures such as chemical composition, molecular weight and molecular weight distribution; higher-order structures such as melting point, glass transition temperature, crystallinity and crystal structure; and surface conditions such as surface area, hydrophilicity and hydrophobicity. As these factors are interrelated in a complicated way, it is not easy to clarify and understand the structure-biodegradability relationships among the wide range of polymeric systems so far.

There are many kind of metabolic mechanisms founded from the living human and animal body. The efforts have been recently directed toward the synthesis of functional biodegradable polymers for biomaterials utilized in the medical application. The Krebs cycle acid derivatives among some natural metabolites are good candidates for the development of biological functional polymers utilized in the biomedical applications such as gene therapy and drug delivery systems. The Krebs cycle acids are due to the main products of the natural processes during the metabolism of the living body. It has been proven that the polyesters prepared from the Krebs cycle acid derivatives are biocompatible and biodegradable. The basis of the scientific idea, the polymeric materials containing biological functions have been developed for the interesting biomaterials to apply to the biomedical application such as cancer therapy and targeting drug delivery systems.

**Biodegradable Polymers from Krebs Cycle Acid Derivatives**

The Krebs cycle acid derivatives have been prepared from the metabolites of the living body. The monomers such as 2-acetoxy succinic acid and 1, 4-butanediol have been synthesized for the development of biodegradable polymeric biomaterials containing biological functions. 1, 4-Butanediol dilactate has been synthesized using L-lactic acid and 1, 4-butanediol diluted in solvent cyclohexane. The synthesis of 2-acetoxy succinic acid has been also carried out using L-malic acid and acetic anhydride. Poly(1,4-butanediol-co-succinate) has been synthesized from 1,4-butanediol and succinic anhydride in solvent p-tolu enesulfonic acid. Poly(1,4-butanediol dilactate-co-succinate) has been also prepared from 1,4-butanediol dilactate and succinic anhydride in the same solvent. Poly(1,4-butanediol dilactate-co-2-acetoxy succinate) has been also polymerized using 2-acetoxy succinic acid with 1,4-butanediol as the same polymerization method of poly(1,4-butanediol dilactate). The cross-linked poly(1,4-butanediol-co-L-malate) have been also synthesized from L-malic acid and 1,4-butanediol by varying functional group ratios. For the characterization of the synthesized polymers, the hydrolytic behaviors in various pH buffer solutions have been tested and their biodegradations by microorganisms have been also studied. The effects of crystallinity and molecular weights of the synthesized polymers on biodegradation have been also investigated. The swelling ratios of the crosslinked copolyesters have been also measured in the various pH solutions on the temperatures such as 20°C, 30°C, and 37°C, respectively. The swelling degree of crosslinked poly(1, 4-butanediol-co-L-malate) is increased with decreasing crosslink density in pH 7.4 aqueous solution. The hydrolysis of the copolyesters proceeds faster with increasing pH aqueous solution. The hydrolytic degradation of poly(1,4-butanediol-co-succinate) has been carried out by stirring dispersion in 0.1 N NaOH alkaline solution at 37°C. The weight loss of poly(1,4-butanediol-co-succinate) reaches up to 85% within two days. The degradation of poly(1,4-butanediol-co-succinate) by actinomyete and bacteria is similar to the sequence of events observed with fungi except longer existence of the crystalline structure. The degradation of higher molecular weight poly(1,4-butanediol-co-succinate) were slower trend to that of lower molecular weight of poly(1,4-butanediol-co-succinate). The crystalline structure of higher molecular weight poly(1,4-butanediol-co-succinate) has been maintained longer period than that of lower molecular weight poly(1,4-butanediol succinate). The biodegradable behaviors of the crosslinked poly(1,4-butanediol-co-L-malate) have been checked using microorganisms such as fungi and bacteria, which have been routinely used in the ASTM procedures for the determination of biodegradation. The degrees of biodegradation after seven weeks have been degraded up to 85% in Aspergillus niger and degraded up to 75% in Pseudomonas fluorescens, respectively.

The effects of the pendant hydrophobic group and crystallinity have been investigated on the poly(1,2-propanediol-co-succinate) and poly(1,3-propanediol-co-succinate). Their morphology changes during biodegradation have been observed using optical microscopy to compare with their biodegradability. The quantitative determination of carbon dioxide, generated during the treatment with the activated sludge, showed that poly(1,3-propanediol-co-succinate) has been biodegraded faster than poly(1,2-propanediol-co-succinate) with the pendant hydrophobic methyl group. The biodegradability for Aspergillus niger to degrade the polymers have been monitored using gel permeation chromatography. The biodegradation of poly(1,2-propanediol-co-succinate) with the biofunctional pendant hydrophobic methyl group has been slower than that of poly(1,3-propanediol-co-succinate). In the crystallinity changes of the polymers during biodegradation, the chain scissions in the crystalline region of poly(1,3-propanediol-co-succinate) proceed faster than those of poly(1,2-propanediol-co-succinate). Based upon the visual observation of their biodegradation, the crystalline structure of poly(1,2-propanediol-co-succinate) retains its crystallinity longer than the similar structure in poly(1,3-propanediol-co-succinate). These biodegradable polymers have
been degraded to the lower molecular weight components depending upon both their hydrophobicity of the chain structures.\textsuperscript{27-29}

**Biodegradable Copolymer Systems Containing Biological Functions**

The block copolymers of L-lactic acid and L-glutamic acid with different biological functions were prepared and characterized for biomedical applications.\textsuperscript{30} Some biodegradable copolymers are of particular interest for biomedical application into tissue engineering and drug delivery systems. Several types of in situ forming biodegradable polymers have been synthesized such as the biodegradable thermosensitive copolymers of poly(D,L-3-methyl glycolide)-co-poly(ethylene glycol)-co-poly(D,L-3-methyl glycolide). The biodegradable polymeric materials consisting of poly(ethylene glycol)-co-poly(lactide) and poly(ethylene glycol)-co-poly(D,L-lactide) star block copolymers have been recently developed.\textsuperscript{6,9} The aqueous poly(ethylene glycol)-block-poly(D,L-lactic acid-co-glycolic acid)-block-ethylene glycol) triblock copolymer solutions are free flowing sols at room temperature, however, a gel of PEG-PLGA-PEG is formed at body temperature near 37°C. The PEG-PLGA-PEG triblock copolymers were prepared by the ring-opening polymerization of DL-lactide and glycolide onto monomethoxy poly(ethylene glycol) followed by coupling of the hydroxyl groups of resulting PEG-PLGA diblock copolymers using hexamethylene disocyanate.\textsuperscript{10} The PEG-PLGA-PEG systems have been recently designed on the basis of the proven biocompatibility of PEG, lactic acid and glycolic acid, which are the final degradation products of these polymers.\textsuperscript{11}

DNA-based tissue engineering for biomedical application has been investigated as a way to grow new tissues and organs. The local delivery of plasmid DNA will allow appropriate levels of transgene expression for a prolonged period. The sustained release of plasmid DNA from biodegradable polymer matrix can lead to the transfection of large number of cells at a localized site, leading to the production of therapeutic proteins needed for tissue regeneration.\textsuperscript{11} The plasmid DNA encoding platelet-derived growth factor has been directly incorporated into biodegradable poly(D,L-lactide-co-glycolide) three-dimensional matrix.\textsuperscript{9} Plasmid DNA was subsequently released from the matrices over a period ranging from days to month in vitro, and led to enhancement of matrix deposition and blood vessel formation in developing tissues in vivo.\textsuperscript{32} The inefficient delivery of growth factors locally in a transient but sustained manner is a major barrier to effective tissue regeneration. The implantation of polymer matrix with plasmid DNA at the site of bone injury was associated with retention and gene expression of the plasmid DNA for at least 6 weeks. Using biocompatible materials for local and sustained-controlled release of plasmid DNA, the delivery systems were developed for tissue engineering.\textsuperscript{33,34}

RNA interference represents a naturally powerful method occurring biological strategy for inhibition of gene expression. It is mediated through small interfering RNAs (siRNAs), which trigger specific mRNA degradation. In mammalian systems, the application of siRNAs is severely limited by the instability and poor delivery of unmodified siRNA molecules into the cells in vivo. Similar strategy has been developed for the construction of a target-specific delivery system of green fluorescent protein siRNA plasmid DNA by utilizing folate-modified cationic low molecular weight poly(ethyleneimine). The application of this system to folate receptor positive cells resulted in a marked reduction of GFP expression. The inefficient delivery of growth factors locally in a transient is a major barrier to effective tissue regeneration. The implantation of polymer matrix with plasmid DNA at the site of bone injury was associated with retention and gene expression of the plasmid DNA for at least 6 weeks. Using biocompatible materials for local and sustained-controlled release of plasmid DNA, the delivery systems were developed for tissue engineering.\textsuperscript{34,35}

On the other hand, self-assembling nanoparticles with siRNA has been constructed with PEI that is PEYlated with an peptide ligand attached at the distal end of poly(ethylene glycol).\textsuperscript{36} The organic-inorganic hybrid nanoparticles entrapping oligodeoxynucleotide or siRNA were prepared through the self-associating phenomenon of the block copolymer, poly(ethylene glycol)-block-poly(aspartic acid), with calcium phosphate. Then, the calcium phosphate core dissociated in the intracellular environment with appreciably lowered calcium ion concentration compared to the exterior, allowing the release of the incorporated oligodeoxynucleotide and siRNA.\textsuperscript{37} Utilizing functional biodegradable polymers in the development of better method for highly efficient delivery of siRNA in a controlled manner, it will be provided as a best RNAi technique for biomedical applications.\textsuperscript{37} Poly(D,L-lactic acid-co-glycolic acid)(PLGA) is a commonly used biodegradable and biocompatible polymer containing biological functions. The PLGA microspheres have been shown to protect DNA from degradation by nuclease.\textsuperscript{38,39} Using a water-in-oil-in-water (W/O/W) double-emulsion and solvent evaporation method, the nanospheres containing plasmid DNA had been prepared. The release kinetics, microsphere size, and encapsulation efficiency of plasmid DNA were found to be dependent on the emulsification methods, water/oil ratio, primary emulsion and the surfactant concentration.\textsuperscript{40} Plasmid DNA was mixed with these nanoparticles and incubated for 1 hr at room temperature. The adsorption of DNA on the surface of the nanoparticle was dependent on the dextran contents in the graft copolymer. The adsorption of DNA on the surface of the nanoparticle was dependent on the dextran contents in the graft copolymer. It has been conjugated polysaccharide-grafted PLL and mixed this with poly(D,L-lactide) to prepare nanoparticles by either solvent evaporation or dialfiltration.\textsuperscript{41} The ionic interaction between DNA and PLL moi-
eties on the nanoparticles is thought to be the main driving force for DNA absorption on the nanoparticles. For the nanoparticles prepared from PLL homopolymer/PLA, the majority of the amino groups in PLL might be interacting with PLA, leading to form adsorption of PLL on the nanoparticle surfaces. The biodegradable copolymer systems containing biological functions can be utilized as more useful biomaterials for biomedical application on the basis of biological adaptability in near future.

References


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