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Functional polypeptide and hybrid materials: Precision synthesis via α-amino acid *N*-carboxyanhydride polymerization and emerging biomedical applications

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ABSTRACT

Polypeptides derived from naturally occurring α-amino acids have emerged as a unique and versatile family of bio-inspired biomaterials that can be tailor-made for varying biomedical applications such as controlled drug release, gene delivery, tissue engineering and regenerative medicine. In contrast to traditional biodegradable polymers such as aliphatic polyesters and polycarbonates, polypeptides are inherently functional, allow precise control over polarity and charges, show excellent stability against hydrolysis, and are prone to rapid biodegradation in vivo by specific enzymes. Ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydrides (NCAs) is the most straightforward and practical approach for large-scale production of high molecular weight polypeptides. In the past decade, a

Abbreviations: AMM, "activated monomer" mechanism; AOB-L-Glu NCA, γ-(4-allyoxylbenzyl)-L-glutamate *N*-carboxyanhydride; APP, 5-(4-aminophenyl)-10,15,20-triphenyl-porphyrin; ATRP, atom transfer radical polymerization; BLA-NCA, β-benzyl-L-aspartate *N*-carboxyanhydride; BLG-NCA, γ-benzyl-L-glutamate *N*-carboxyanhydride; Boc, tert-butoxycarbonyl; BPA, 2-bromo-*N*-(2-aminethyl)-2-methylpropionamide; Bpy, 2,2′-bipyridine; BSA, bovine serum albumin; CCA, cis-1,2-cyclohexanedicarboxylic acid; CLG-NCA, γ-chloropropyl-L-glutamic acid *N*-carboxyanhydride; CLSM, confocal laser scanning microscopy; COD, 1,5-cyclooctadiene; CP, chloropropanyl; CRP, controlled radical polymerization; Cys, L-cysteine; DDT, dodecanethiol; DHBC, double hydrophilic block copolymer; N^{α},N^{ε}-diFmoc Lys, N^{α},N^{ε}-di(9-fluorenylmethoxycarbonyl)-L-lysine; DOPA, L-dihydroxylphenylalamine; DOX, doxorubicin; DTT, dithiothreitol; EG_2-Lys NCA, N^{ε}-2-(2-(2-methoxyethoxy)ethoxyl)acetyl-N^{α}-Z-L-lysine *N*-carboxyanhydride; EO_2MA, 2-(2-methoxyethoxy)ethyl methacrylate; EPR, enhanced permeability and retention; FITC, fluorescein isothiocyanate; Fmoc, 9-fluorenylmethoxycarbonyl; F-PBA, 3-fluoro-4-carboxyphenylboronic acid; GSH, glutathione; HA, hydroxyapatite; HEMA, 2-hydroxylethyl methacrylate; HMDS, hexamethyldisilazane; Hyd, hydrazide; LA, lipoic acid; LCST, lower critical solution temperature; Leu-NCA, L-Leucine *N*-carboxyanhydride; NAM, "normal amine" mechanism; NBC-NCA, *S*-(*o*-nitrobenzyl)-L-cysteine *N*-carboxyanhydride; NGF, nerve growth factor; NMP, nitroxide-mediated polymerization; *N*-TMS, *N*-trimethylsilazane; Nvoc, 6-nitroveratryloxycarbonyl; OEG, oligo(ethylene glycol); PAA, poly(L-aspartic acid); PAla, poly(L-alanine); PAMAM, poly(amido amine); PAOBLG, poly(γ-(4-allyoxylbenzyl)-L-glutamate); PAPB, polyaspartate modified with 4-phenyl-butanol; PAPLG, poly(γ-azidopropylglutamate); PArg, poly(L-arginine); PAsp, poly(L-aspartic acid); PAsp(DET-Aco), poly(*N*-(*N*′-((*N*″-cis-aconityl)-2-amnoethyl)-2-aminoethyl) aspartmide); PAsp(EDA-Cit), poly(*N*-(citraconyl-2-aminoethyl) aspartamide); PBLA, poly(β-benzyl-L-aspartic acid); PBLG, poly(γ-benzyl-L-glutamic acid); PCys, poly(L-cysteine); PDI, polydispersity index; PDMAEMA, poly(2-(dimethylamino)ethyl methacrylate); PDMAM, poly(*N*,*N*′-dimethylacrylamide); PDTA, 2-(2-pyridinyldithio) ethylamine hydrochloride salt; PEG, poly(ethylene glycol); $P(EG_2$-Lys), poly(N^{ε}-2-[2-(2-methoxyethoxy) ethoxyl] acetyl-L-lysine); PEO, poly(ethylene oxide); PEI, polyethylenimine; PGlu, poly(L-glutamic acid); PHArg, poly(L-homoarginine); Phe-NCA, L-phenylalanine *N*-carboxyanhydride; PHis, poly(L-histidine); PLeu, poly(L-leucine); PLGA, poly(lactide-co-glycotide); PLLA, poly(L-lactide); PLys, poly(L-lysine); PMPA, poly((3-morpholinopropyl)aspartamide); PNBC, poly(*S*-(*o*-nitrobenzyl)-L-cysteine); PNIPAM, poly(*N*-isopropylacrylamide); PPhe, poly(L-phenylalanine); PPLG-NCA, γ-propargyl-L-glutamate *N*-carboxyanhydride; PPO, poly(propylene oxide); PS, polystyrene; PTFALys, poly(trifluoroacetyl-L-lysine); PTMC, poly(trimethylene carbonate); PVal, poly(L-valine); PVBLG, poly(γ-(4-vinylbenzyl)-L-glutamate); RAFT, reversible addition-fragmentation chain-transfer; ROP, Ring-opening polymerization; SPPS, solid phase peptide synthesis; tBMLC, *S*-tert-butylmercapto-L-cysteine; TFA, trifluoroacetyl; TFA-Lys NCA, ε-trifluoroacetyl-L-lysine *N*-carboxyanhydride; TMS, trimethylsilyl; 4-VB, 4-vinylbenzyl; VB-Glu NCA, γ-(4-vinylbenzyl)-L-glutamate *N*-carboxyanhydride; VSCys-NCA, vinyl sulfone-substituted L-cysteine *N*-carboxyanhydride; Z, benzyloxycarbonyl; ZLys-NCA, *N*-benzyloxycarbonyl-L-lysine *N*-carboxyanhydride.

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Biomaterials
Drug release
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Tissue engineering

remarkable progress has been made in controlled NCA polymerization, which offers an unprecedented access to precision polypeptide and hybrid materials by combining with living radical polymerization, click chemistry, and/or post-polymerization modification. Notably, several micellar anti-cancer drugs based on poly(ethylene glycol)-polypeptides have been already advanced to the clinical evaluation. In this review paper, we give an overview on de novo design, controlled synthesis and emerging biomedical applications of functional polypeptide and hybrid materials.

Contents

1. Introduction

Proteins and oligopeptides produced by living organisms are the most versatile biological materials that provide structural and mechanical support to cells, tissues and organs (e.g. actin, myosin, collagen), catalyze various biochemical reactions (e.g. enzymes, glutathione), and regulate cell signaling, cell adhesion, and immune responses (e.g. cell surface markers, receptors, peptide hormones) [1–4]. The vastly different functions of proteins and oligopeptides originate from a wide choice of α-amino acid monomers as well as control of peptide sequences [5]. In the past decade, significant effort has been directed to the development of de novo oligo- and polypeptides that mimic natural proteins possessing excellent biocompatibility and biodegradability in vivo for diverse biological, medical and pharmaceutical applications [5–11].

In comparison with aliphatic polyesters and polycarbonates that are the prime synthetic biodegradable polymers currently applied for various biomedical applications, polypeptide materials have several potential advantages, e.g. (i) they are inherently functional providing a variety of reactive groups ranging from hydroxyl, carboxyl, thiol, to amino groups, which render them particularly appealing in design and development of multi-functional bioactive biomaterials; (ii) they offer excellent control over hydrophilic and hydrophobic balance by constituent α-amino acid monomers, compositions, sequences and molecular weights, which allow formation of essentially any supramolecular structures spanning from nanoscale, microscale, to macroscale (Fig. 1); (iii) they can be designed with varying charged groups including imidazole in histidine and guanidino in arginine that play an indispensable role in biological interactions in vivo including