Progress in Polymer Science 80 (2018) 94–124

Contents lists available at ScienceDirect

Progress in Polymer Science

journal homepage: www.elsevier.com/locate/ppolysci

Protein-mimetic peptide nanofibers: Motif design, self-assembly synthesis, and sequence-specific biomedical applications

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ARTICLE INFO

Article history:
Received 26 July 2016
Received in revised form
13 December 2017
Accepted 13 December 2017
Available online 16 December 2017

Keywords:
Protein-mimetic peptide
Nanofibers
Motif design
Self-assembly
Biomedical application

ABSTRACT

The design and fabrication of self-assembled peptide nanostructures offer an amazing platform for creating functional nanomaterials for various biomedical applications. Utilizing the mechanical and biological advantages of the protein-mimetic peptide (PMP) system, and combining self-assembled PMP nanofibers with other nanomaterials like nanoparticles, the fabricated PMP-based hybrid fibrous nanostructures can serve as promising candidates for advanced technological applications. In this review, we present the design, synthesis, modification, and fabrication of PMP nanofibers by mimicking the properties and functions of several types of proteins, including extracellular matrix proteins, silk proteins, amyloid proteins, and heparin. The sequence and motif design of PMPs, and the relationships between the design of PMP monomers and the fabrication of functional fibrous biomaterials are introduced and discussed. Furthermore, we summarize a basic classification of various peptide motifs, and provide some instructions for the function-based design of peptide nanostructures, in which some issues on the motif design and function tailoring are discussed. Finally, the recent advances in the PMP nanofiber-based functional nanomaterials in biomineralization, cell culture, tissue regeneration, drug delivery, hemostasis, bioimaging, and biosensors are presented in detail. We believe that this review will be very helpful for researchers to understand the property-specific molecular design, controllable supramolecular self-assembly, and motif-specific applications of both peptides and proteins.

Contents

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https://doi.org/10.1016/j.progpolymsci.2017.12.001
0079-6700/

1. Introduction

Supramolecular self-assembly is an important and effective strategy to form a large and organized bimolecular superstructure, by which biomolecules can achieve their bioactive functions. For example, aptamers can assemble to RNA and DNA, to carry genetic information into chromosomes; amino acids can assemble to secondary peptide structures and then fold into a more complex protein molecule. The natural self-assembly and disassembly of biomolecules develops bioactive macromolecular systems with enormous complexity, able to achieve most of the *in vivo* functions for organisms. Inspired by the self-assembly of biomolecular building blocks, numerous artificial supramolecular systems have been designed and created over the past few decades [1–4]. It is well known that proteins with high molecular weight, diverse functions, and high complexity are difficult to synthesize and simulate at the molecular level, while peptides possess much more potential for theoretical and experimental investigations of the partial functions of proteins. Thanks to the rapid development of peptide synthesis techniques, it is possible to synthesize peptides with the desired amino acid sequence, expectable bio-properties, and controllable self-assembly ability. Peptides created by mimicking the functions and properties of natural proteins, called protein-mimetic peptides (PMPs) [5,6], have developed into a versatile platform for building multifunctional biocompatible materials.

From the biological point of view, PMPs offer an alternative opportunity to understand and utilize proteins in an indirect way. It is known that the natural proteins organized through long-time evolution and *in vivo* formation. Therefore, their highly ordered superstructures and attractive functions provide inspirations for designing artificial nanostructures with high biocompatibility and nature-similar mechanical characteristics. Previously, more and more sequences of proteins and their self-assembly properties have been revealed, but an understanding of the inner relations between sequences and functions of amino acids remains a great challenge. PMPs with designed motifs, structures, and functions that relate to the properties of whole proteins may lead to the potential understanding of the inner folding, unfolding, and aggregation mechanisms of proteins, including i) the inner relations between amino acid sequence and protein functions, ii) the relations between sequence and self-assembly formation, and iii) the potential connections between protein aggregation and controlled self-assembly of peptides. On the other hand, the accidental misfolding of proteins and subsequent protein aggregation may be implicated in severe diseases, such as Alzheimer's, Huntington's, Parkinson's, and prion diseases [7–9]. For example, Alzheimer's disease is caused by the aggregation of misfolded proteins into amyloid-β plaques, leading to the formation of protein fibrils and following neurodegenerative disorders [8]. To inhibit the protein fibrillation, numerous studies have been conducted to analyze both amino acid sequences and structures of proteins to understand the protein folding, misfolding, aggregation, and corresponding self-assembly mechanisms [9]. Therefore, studying the controllable self-assembly of PMPs and the formation of PMP nanofibers may significantly contribute to the evolution of understanding the inner mechanisms of protein fibrillation and the rapid development of novel biomedical applications of PMPs.

It is possible to determine some short amino acid sequences that relate to the main functions and properties of proteins by the structural analysis of proteins. When a segment of amino acid sequence is associated with specific functions, the sequence can be defined as a motif. Nature defines many structural and biofunctional motifs through billions of years of evolution, and there are many natural motifs having been observed in natural proteins. One motif may exist in many different proteins containing the same sequence, displaying similar functions. As more and more structures and functions of peptide motifs have been investigated and identified, they have been regarded as potential building blocks for creating peptide-based functional materials. To construct peptide nanofibers and three-dimensional (3D) nanofibrous scaffolds, a peptide monomer often consists of both structural building block(s) and bioactive motif(s). The motif of a peptide determines the occurrence, driving forces (including non-covalent forces like ionic force, hydrogen bond, hydrophobic force, and π-π stacking), and ultimate formation of peptide nanofibers [10]. These driving forces offer a mild and bottom-up approach to fabricate various supramolecular nanostructures.

Previously, a large number of self-assembled peptide superstructures have been reported, including peptide nanofibers, nanotubes, and nanovesicles [11,12]. This review is focussed on