Nano Today (2016) 11, 41—60

Available online at www.sciencedirect.com

ScienceDirect

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

REVIEW

Self-assembled peptide-based nanostructures: Smart nanomaterials toward targeted drug delivery

Neda Habibi[a], **Nazila Kamaly**[b], **Adnan Memic**[c], **Hadi Shafiee**[a,*]

[a] *Division of Biomedical Engineering, Division of Renal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02139, USA*
[b] *Laboratory of Nanomedicine and Biomaterials, Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA*
[c] *Center for Nanotechnology, King Abdulaziz University, Jeddah 21589, Saudi Arabia*

Received 7 January 2016; received in revised form 12 February 2016; accepted 15 February 2016
Available online 11 March 2016

KEYWORDS
Self-assembled;
Peptide;
Nanostructure;
Drug delivery;
Smart nanomaterials

Summary Self-assembly of peptides can yield an array of well-defined nanostructures that are highly attractive nanomaterials for many biomedical applications such as drug delivery. Some of the advantages of self-assembled peptide nanostructures over other delivery platforms include their chemical diversity, biocompatibility, high loading capacity for both hydrophobic and hydrophilic drugs, and their ability to target molecular recognition sites. Furthermore, these self-assembled nanostructures could be designed with novel peptide motifs, making them stimuli-responsive and achieving triggered drug delivery at disease sites. The goal of this work is to present a comprehensive review of the most recent studies on self-assembled peptides with a focus on their ''smart'' activity for formation of targeted and responsive drug-delivery carriers.

Introduction

Molecular self-assembly is the spontaneous formation of ordered structures. These processes occur under thermodynamic and kinetic conditions that are a consequence of specific and local molecular interactions [1]. Hydrogen bonding, hydrophobic interactions, electrostatic interactions, and van der Waals forces combine to maintain molecules at a stable low-energy state. Self-association to form hierarchical structures at both nano and/or microscales occurs in order to achieve minimal energy state [2].

Self-assembly occurs spontaneously in nature during protein folding, DNA double-helix formation, and the formation

* Corresponding author.
E-mail address: hshafiee@research.bwh.harvard.edu (H. Shafiee).

http://dx.doi.org/10.1016/j.nantod.2016.02.004
1748-0132/

of cell membranes [3]. Self-assembling nanostructures fabricated from natural biomolecular building blocks such as amino acids are highly preferable to their synthetic self-assembled monolayer (SAMs) alternatives [4] due to their biocompatibility and ease of ''bottom-up'' fabrication [5]. Although several self-assembly platforms have been introduced for biomedical applications, self-assembling peptides remain the most attractive soft biomaterial option for several reasons:

I. Peptides are easily synthesized using solid-phase methods, which allows for sequence-specific modifications at the molecular level [6].
II. Additional peptide functionalization can easily be performed by introducing compounds such as antibodies, enzymes, magnetic particles, or fluorescent compounds to the peptide structure [7].
III. Custom supramolecular structures can be designed through engineering of self-assembled peptide building blocks [6].
IV. Naturally occurring self-assembly motifs present in proteins such as α-helices, β-sheets, and coiled-coils can be used to drive the self-assembly process [8].
V. Peptides are the most attractive biomaterials for regenerative scaffolds, since the main ''signaling language'' in the extracellular matrix (ECM) is mediated via peptide epitopes [9].
VI. Self-assembly is important in cell-penetrating peptide (CPP) mechanisms, which play a major role in introducing drugs inside cell membranes and translocating genes inside a nucleus [10].

Though there have been several reviews on peptides and their self-assembling properties, most are focused on tissue engineering rather than drug-delivery applications [11—13]. Therefore, there is a lack of comprehensive review on the use of self-assembled peptides as ''smart'' drug-delivery platforms that are capable of specific tissue or cellular targeting, and release of therapeutic components in response to environmental cues. The focus of this review is on factors that govern self-assembled peptide (SAP) targeting activity and controlled-release properties. We aim to provide insight into how SAPs can be engineered into smart drug-delivery platforms that exhibit enhanced biological functions, such as intracellular and targeting uptake, controlled release, and reversible enzymatic hydrogel formation. Finally, we also cover a broad range of self-assembled peptides and peptide derivatives. We believe that this review highlights the importance of self-assembled peptide nanostructures for nanomedicine applications and can facilitate further knowledge and understanding of these nanosystems towards clinical translation of such therapeutic materials.

Self-assembled peptides

Self-assembled peptides were categorized into peptides and peptide derivatives according to their building blocks. In the section on peptides, naturally occurring peptide motifs (α-helical, β-sheets, β-hairpins, etc.) are discussed and in the section on peptide derivatives, self-assembled peptides such as peptides amphiphiles (PAs) with alkyl chains are introduced. Relevant examples are presented to highlight the importance of these structures as basic building blocks for targeted drug-delivery carriers.

Peptides

α-Helical peptide/coiled coil

For decades it has been known that physical and biological properties can promote the formation of helical structures. However, with the advent of material design, only recently have key molecules been discovered in order to incorporate these helical structures into biomaterials.

The α-helical structure results from hydrogen bonding between backbone amides that form right-handed α-helices with a periodicity of 3.6 residues per turn. Interaction with other helices are possible through the side chains of the amino acids involved, as they protrude outwards from the helix. However, it is challenging to produce these structures in practice, in part because longer lengths (20—30 amino acid) are usually required to establish stable α-helical interactions.

Coiled-coil structures are formed through the assembly of α-helices into higher ordered structures. These architectures form due to the repeated pattern of hydrophobic and charged amino acid residues. In 2009 Smith et al. reported a self-assembled hydrogel [14]. This novel design consisted of two complementary leucine-zipper peptides (SAF-p1 and SAF-p2), which co-assembled into a sticky-ended dimer with complementary overhanging ends. Multiple weak interactions between the fibers prompted the formation of the hydrogel, which was shown to support PC12 cell adhesion and proliferation into neurons [14].

β-Sheet

β-Sheets are the most common natural motifs that can be used in driving the self-assembly of peptides. β-Sheets consist of sequences that possess alternating hydrophobic and hydrophilic amino acids, providing the peptide backbone an amphiphilic property that directs formation of β-sheets. Fishwick et al. proposed that the P11-II peptide sequence QQRFQWQFEQQ and its derivatives form twisted β-sheet tapes, naturally reinforced by the amphiphilic nature of the sequence. These β-sheet tapes are triggered to form hydrogels by screening the charges between fibers [15].

β-Hairpin

Orientation of two β-sheets in anti-parallel directions results in formation of β-hairpins in proteins. Shneider et al. [16] proposed a β-hairpin structure design with the sequence VKVKVKVKVDPPTKVKVKV, where DP is an enantiomer of proline. This peptide possesses an alternating hydrophilic-hydrophobic motif and intermittent tetrapeptide (-VDPPT-) intended to form a type II′ turn structure. This design allows intra-molecular folding and β-sheet formation, yielding a ''hairpin'' structure that can subsequently associate into higher-order fibers and self-supporting hydrogels when the pH is raised. These structural designs were used to form responsive hydrogels, linking pH intra-molecular folding to self-assembly.