Self-Assembling Peptide

Subjects: Others

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Self-assembling peptides are biomedical materials with unique structures that are formed in response to various environmental conditions. Governed by their physicochemical characteristics, the peptides can form a variety of structures with greater reactivity than conventional non-biological materials. The structural divergence of self-assembling peptides allows for various functional possibilities; when assembled, they can be used as scaffolds for cell and tissue regeneration, and vehicles for drug delivery, conferring controlled release, stability, and targeting, and avoiding side effects of drugs. These peptides can also be used as drugs themselves. We describe the self-assembling peptide sequences and resultant nanostructures used for disease treatments.

Keywords: peptide ; self-assembly ; nanostructure ; disease

1.Introduction

The building blocks discussed above have been used to produce various types of structures based on material properties and environmental factors. Over the last few decades, the practical application of peptide-based self-assembled structures has been attempted widely. Table 1 summarizes nanostructures formed by particular self-assembling peptide blocks and their applications for specific biomedical uses.

Table 1. List of self-assembling peptide sequences and resultant nanostructures used for disease treatment.

Structure	Sequence	Applications	Reference
Nanofibers	VEVK9 (VEVKVEVKV) and VEVK12 (VEVKVEVKVEVK)/combined with RGD	Increase fibroblast migration	[1]
	V3A3E3 (VVVAAAEEE)	Stem cell culture and differentiation	[2][3]
Nanotubes	Heparin-binding peptide amphiphile (HBPA)	Hierarchical structure	[4][5]
	Q11 (QQKFQFQFEQQ)	Endothelial cell proliferation	[6]

	Lyp-1 (CGNKRTRGC)	Increase drug cellular uptake	[7]
	MAX8 (VKVKVKVKV^{D}PPTKVEVKVKV)	Drug delivery	[8]
	RADA16 with LRKKLGKA	Vascular endothelial growth factor (VEGF) delivery to the myocardium	[9]
Nano particle, vesicle, micelle, suspension	Tat/Tat combined with PEG/Cholesterol	Cross blood brain barrier (BBB)drug delivery	[10][11]
	cRGDfK	Drug targeting	[12]
	C16V2A2E2K(Hyd)	Drug stabilization	[13]
	V6K2(VVVVVVKK) combined with PLA	Drug delivery	[14]
	EAK16II (AEAEAKAKAEAEAKAK)	Drug stabilization	[15]
	RADA16I (RADARADARADARADA)	Controlled drug release	[16][17]
	RADA16I (RADARADARADARADA)	Hepatocyte regeneration	[18][19]
	RADA16 II (RARADADARARADADA)	Neuron regeneration	[20]
	RADA16-I combined with RGD motif	Neuron regeneration	[21][22]
Hydrogel	RADA16-I combined with RGD motif	Ligament regeneration	[23]
	KLD12 (KFDLKKDLKLDL)	Hepatocyte regeneration	[18]
	KLD12 (KFDLKKDLKLDL)	Chondrocyte regeneration	[24][25]
	KFE8 (FKFEFKFF)	Hepatocyte regeneration	[18]
	FEFEFKFK octarepeat	Extracellular matrix (ECM) accumulation	[26]

2. Application in Cancer Treatment

As a conventional cancer treatment, chemotherapy is fairly successful, but the off-target side effects causing damage to healthy cells and unavoidable development of multi-drug resistance are problematic[27][28]. The response of self-assembling peptides to environmental conditions may offer a means to prevent the aforementioned issues, because the tumor environment has a lower pH and higher temperatures than normal tissues. Thus, self-assembling peptides are well suited for controlled release or targeting of anticancer drugs to tumor sites[29] .

2.1. Targeting

Chemotherapy in conventional cancer treatment is not only targeted to cancer cells, but also affects normal cells that are active in division and proliferation, such as bone marrow, hair, the mucous membrane of the gastrointestinal tract, and reproductive cells. To minimize the nonselective side effects, a specific peptide sequence or motif can be used in

chemotherapy. Peptides designed as nanoparticles for targeting cancer cell surfaces or tumor vasculature in chemotherapy can be used to minimize systemic drug exposure and increase efficiency[30]. One of the cancer-targeting sequences, RGD, which binds to integrin, originates from a cell surface glycoprotein. RGD peptides can be linked to self-assembling peptides and increase the targeting effect of therapeutic drugs[31]. Furthermore, cyclic RGD increases binding affinity to integrins and is helpful in targeting drugs to cancer cells. Murphy et al. showed that cyclic RGDfK used to increase doxorubicin targeting suppressed growth of the primary tumor and prevented metastasis[12]. Another cancer-targeting peptide is the peptide Lyp-1, -CGNKRTRGC-, a nine-amino acid cyclic peptide that recognizes lymphatic metastatic tumors and exerts cytotoxic activity. LyP-1-conjugated PEG–PLGA nanoparticles (LyP-1-NPs) showed increased cellular uptake, by up to 4–8-fold in vitro and in vivo compared with PEG–PLGA nanoparticles without Lyp-1. LyP-1-NPs showed good targeting efficiency to cancer cells in vitro and to metastatic foci in vivo[7].

2.2. Drug Delivery

By modulating the properties of self-assembling peptides, drug release rates can be efficiently controlled. Ketone-containing drugs linked to peptide amphiphiles can be sustainably released at physiological pH. For example, doxorubicin or paclitaxel containing ketone functionality allows covalent tethering between the drug and peptide amphiphile via addition of a hydrazino acid to a lysine ε-amine[13]. In a study from the Stupp group, the peptide amphiphile C16V2A2E2K(Hyd) and its modifications were successfully bound to the ketone-containing fluorescent compound, Prodan. The release rate was dependent on the packing density, the order of the hydrophobic peptide amphiphilic core, and the β-sheet character of the peptide. It can also be controlled by chemical properties (Log P, pKa, pI, presence of aromatic rings, and steric hindrance) and by the solvent release[32]. RADA16 was also used in hydrophobic drug delivery and for self-assembling hydrogels. The diffusion properties of pindolol, quinine, and timolol maleate, through RADA16, showed sustained, controlled, reproducible, and efficient drug release[16][17]. RADA16-X controls the release of hydrophobic antitumor drugs and effectively inhibits the growth of a breast cancer cell line[33]. In this case, hydrogels with a higher peptide concentration have a longer release half-life and could block tumor cell proliferation more effectively.

As drug delivery carriers, self-assembling peptides offer many advantages, such as high efficiency of drug loading, a low ratio of drug loss, and high stability that avoids body clearance[34]. For example, EAK-16II can stabilize ellipticine, a hydrophobic anticancer drug, and form microcrystal suspensions in aqueous solutions. In particular, it is an ionic-complementary peptide that does not cause an immune response when applied to animals[15]. Curcumin, which has anti-inflammatory and antitumorigenic properties, has low water solubility and bioavailability, and is therefore difficult to use for therapeutic purposes. Self-assembling peptide hydrogels, such as the MAX8 (VKVKVKVKV^{D}PPTKVEVKVKV-NH2) peptide, can be an effective vehicle for the delivery of curcumin[8]. This peptide makes β-hairpin hydrogels for injectable agents to provide local curcumin delivery. The study with a medulloblastoma cell line confirmed that the encapsulation of curcumin with a hydrogel did not interfere with its drug activity. Peptide-based nanostructures made from polylactide (PLA) and VVVVVVKK (V6K2) are also used for the drug delivery of doxorubicin and paclitaxel[14]. The release of doxorubicin from PLA–V6K2 nanoparticles was slower than that from PLA–ethylene glycol nanoparticles. In addition, PLA–V6K2 nanoparticles showed a significantly increased cellular uptake rate with no induction of cytotoxicity in marrow stromal cells. However, it was more toxic to the 4T1 mouse breast carcinoma cell line than free doxorubicin. Moreover, PLA–V6K2 nanoparticles exhibited higher tumor toxicity and lower host toxicity in syngeneic breast cancer cells inoculated in mice, suggesting efficient drug delivery with selective toxicity.

3. Application in Regenerative Medicine

Regenerative medicine requires biocompatible scaffolds to increase cell engraftment and improve functionality, as well as to enhance cellular delivery processes. In recent years, engineering of nanostructures formed by self-assembling peptides can function as a scaffold in vivo.

3.1. Self-Assembling Peptides for Hepatocyte Regeneration

The liver is the only regenerative visceral organ in mammals. Self-assembled peptide scaffolds can assist cell growth with increased implantation rate, resulting in fully differentiated hepatocytes. RADA16-I peptide was used for the 3D culture of Lig-8 liver progenitor cells. The functional differentiation of hepatocytes by RADA16 scaffold was confirmed by the successful induction of CYP1A1 and CYP1A2 after hepatocyte cluster formation[18]. In addition, strongly hydrophobic peptide amphiphiles, such as KLD12 (AcN-KLDLKKDLKLDL-CNH2) or KFE8 (FKFEFKFE), resulted in greater stiffness of scaffold and increased cell growth, with a better differentiation rate compared with RADA16. From these results, the stiffness of self-assembled peptide scaffolds was shown to be one of the important factors for hepatocyte differentiation. An in vivo experiment with another hepatocellular carcinoma cell line, HepG2, also showed that RADA 16-I had a positive effect on cell growth and cluster formation[19]. RADA16 and other peptides combined with RADA16, such as RADA16-

GRGDS, showed that myofibroblast replacement and hepatocyte cell proliferation were enhanced in vivo by RADA16 with an extended motif[35]. This result suggests that self-assembled peptide structures binding to other ECM motifs may be effective for liver tissue regeneration, although the enhancement of liver tissue regeneration requires various other forms of combined motifs.

3.2. Self-Assembling Peptides for Neuronal Regeneration

The regeneration or rehabilitation of neuronal tissue is difficult, owing to the characteristics of neuronal cells. Neuronal cells grow slowly, are difficult to differentiate, and have great networking complexity in vivo. Therefore, it is difficult to recover from ischemia or stroke damage in the brain, which manifest as neural function loss and cell death. Moreover, clinical conditions with chronic or idiopathic neuronal degeneration, such as Alzheimer's disease, Parkinson's disease, and prion disease, remain incurable[36].

Previous studies using RADA16-I and II as scaffolds in immature mouse cerebellum and rat hippocampus cells showed successful extensive neuron outgrowth. This growth was sustained for more than 4 weeks and resulted in the formation of an active synaptic connection[20]. The -IKVAV- penta-peptide combined with -Glu- and A4G3-alkyl residues is another example of using self-assembling peptides in neuronal cell regeneration, because the -IKVAV- peptide, a laminin epitope, was previously shown to promote neurite sprouting and growth. This peptide not only increased the fibril formation of self-assembled structures, but also improved cell growth, promoted neuronal cell differentiation, and inhibited astrocyte differentiation[37]. In addition, -SKPPGTSS, -PFSSTKT-, and RGD motifs combined with the RADA16-1 peptide increased the levels of nestin, β-tubulin, and other neuronal markers[21][22]. The self-assembling peptide nanofiber scaffold (SAPNS) composed of RADA16 resulted in reconnection of the injured spinal cord and facilitated axon regeneration and, eventually, locomotor functional recovery in animal models of spinal cord injury and acutely injured rat brain[38].

3.3. Self-Assembling Peptides for Cartilage Regeneration

Traumatic injury or degenerative articular cartilage defects require repair, with the deposition of ECM on the bone or previously existing cartilage. For successful cartilage regeneration, the newly assembled ECM must be combined with the remaining cartilage to achieve stable elastic restoration. The self-assembling peptide hydrogel scaffold is useful as a template for chondrocyte proliferation and ECM accumulation. In an experiment using the self-assembling KLD-12 peptides, chondrocytes showed increased proliferation and greater accumulation of cartilage-specific ECM molecules, such as proteoglycans, in the hydrogel scaffold[24][25], indicating that a highly porous hydrogel can be applied as a good scaffold for cartilage regeneration. In another report about alternating polar and non-polar amino acid residues, the -FEFEFKFK- octarepeat peptide formed β-sheet-rich nanofiber scaffolds and improved chondrocyte differentiation and ECM accumulation efficiency compared with previously studied RADA16 or KLD-12[26].

3.4. Self-Assembling Peptides for Vascular Regeneration

Vascular regeneration aims to reshape blood vessels of various sizes and shapes, from microvascular to aortic[39]. Self-assembling peptides are also effective in vascular tissue regeneration and work as a scaffold to influence cell alignment, adhesion, and differentiation, and to promote better endothelization. In the study of Stupp et al.[4][5], peptide amphiphiles with a heparin-binding motif showed increased hierarchical structures and promoted rapid angiogenesis through heparin-binding growth factors involved in angiogenesis signaling. A Q11 (Ac-QQKFQFQFEQQ-Am) self-assembling peptide gel also promoted the proliferation of human umbilical vein endothelial cells and the expression of CD31 (PECAM), a vein endothelial cell marker, on the surface of these gels[6]. Both of these designed peptide structures helped the delivery and accumulation of angiogenic growth factors, such as VEGF and heparins, at the vessel regeneration site. RADA16 combined with the heparin binding domain motif sequence LRKKLGKA also increased VEGF delivery after myocardial infarction, and eventually improved cardiac function[9].

4. Other Applications

The BBB is the most challenging biological membrane encountered in drug delivery. Following the development of peptide science, researchers have tried to design self-assembling peptides to cross the BBB. The Tat (YGRKKRRQRRR) peptide found in a viral protein is known to penetrate the plasma membrane of cells, suggesting its function as a carrier to deliver drugs across the biological membrane. The Tat-polyethylene glycol-b-cholesterol (Tat-PEG-b-col) peptide, which forms micelles, allows antibiotics to migrate through the BBB [95]. Self-assembled polymersomes formed with lactoferrin-modified polyethylene glycol-poly ($_{D,L}$-lactic-co-glycolic acid)(PEG–PLGA) successfully deliver humanin, a neuroprotective peptide, across the BBB in a rat model of Alzheimer's disease[11].

Antimicrobial cationic peptides are used as peptide drugs to treat bacterial infection or prevent it. Antimicrobial peptides are amphipathic and destroy the cell membrane. For example, C16-KKK showed stronger antimicrobial activity than gentamicin in *E. coli* 25922[40]. In another study, an antimicrobial cationic drug combined with RADA16 was shown to be released until 28 days after treatment[41]. Moreover, it also inhibited the growth of *Staphylococcus aureus*. Furthermore, cholesterol-conjugated Tat peptide (cholesterol–CG3R6TAT) formed nanoparticles that showed strong antimicrobial activity. It inhibited the growth of various types of Gram-positive bacteria, fungi, and yeast. These nanoparticles were able to cross the BBB and successfully treat *Staphylococcus aureus*-induced meningitis in rabbit.

The design of the self-assembling peptide scaffolds VEVK9 (Ac–VEVKVEVKV–$CONH_2$), VEVK12 (Ac–VEVKVEVKVEVK–$CONH_2$) and variants modified with RGD or a cell adhesion sequence resulted in a significant acceleration of fibroblast migration[1]. Periodontal ligament fibroblasts also significantly increased the production of Type I and Type II collagen upon culture with RADA16 combined with RGD and a laminin cell adhesion motif[23]. These results suggest that designed self-assembling peptides can regulate fibroblast cellular regeneration or reconstitution of the ECM. They can improve the skin or fibroblast tissue regeneration in scars or wound healing.

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