

**Review Article**

The Potential Role of the Peptide Amphiphiles in Targeted Drug Delivery to Tumors

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Abstract: Background: Targeted drug delivery approaches are intended to increase the effectiveness of drugs by carrying large doses of chemotherapeutic agents to the cancer cells and reduce negative side effects. Self-assembly of peptides can organize molecules into stable and well-defined nanostructures being very attractive for many biomedical applications including drug delivery. Objective: The objective of the current mini-review is to investigate the self-assembly behavior of peptide amphiphiles as nanocarriers under different biological factors in the tumor microenvironment. Method: Data from a range of resources like Google Scholar, PubMed, Medline, Scopus and Elsevier, and other valued journals have been reviewed carefully. Results: Structural changes of peptide amphiphiles in response to tumor microenvironment or tumor-specific enzymes are the promising trend, allowing the development of targeted therapy with high efficiency. However, significant improvement in cytotoxicity is achieved when peptide amphiphiles are designed in such a way to respond to multiple stimuli in tumor microenvironments. Conclusion: A multi-disciplinary research area may permit both to reduce the off-target side effects of anticancer drugs and achieve triggered drug delivery at disease sites.

Keywords: Peptide Amphiphiles, Tumor Microenvironment, Targeted Delivery, Nanocarriers

1. Introduction

The most common treatment for cancer diseases is still conventional chemotherapy. However, due to the limited accessibility of drugs to the tumor tissue and non-specific distribution of drugs in body tissue, its success level remains low [1]. Nanocarriers offer great improvements, including carrying large doses of chemotherapeutic agents into cancer cells, while protect normal tissues from adverse side effects [2]. Among various nanocarriers, self-assembled peptide nanostructures have attracted considerable attention as suitable functional materials in drug delivery application [3]. Typically, peptide amphiphiles contain a hydrophilic head at the other structure that serve as a bioactive sequence and a hydrophobic tail incorporates self-assembly of these amphiphiles into nanostructures with diverse functions [4-7]. Precise manipulation of amino acid properties in the

design of peptides enables initiation of self-assembly to form novel functional biomaterials [8]. As a result of the peptide amphiphiles self-assembly, various types of nanoparticles such as tubes, vesicles, and hydrogels are formed that each type is suitable for delivery of specific kinds of anticancer agents [9]. The *formation* of well-ordered *nanostructures* via self-assembly of peptide amphiphiles makes them a good candidate for controlling drug release and improving cellular uptake being attributed in response to the stimulus of the physiological environment in cancer tissues [9, 10]. Peptide amphiphiles with specific bioactivities including receptor binding, structural sensitivity to changing local environment resulted in decreasing toxic side effects while maintaining high drug efficacy [11]. This mini review summarizes self-assembly of peptide amphiphiles in response to stimuli in the tumor microenvironment.

2. Material and Methods

In this mini review, we searched different keywords including peptide amphiphiles, tumor microenvironment, and targeted delivery, nanocarriers in Google Scholar, PubMed, Medline, Scopus and Elsevier. Finally 31 entitled articles were chosen and organized in three parts: environment-responsive peptide amphiphiles, targeting the surface of tumors by peptide amphiphiles and combination therapy.

3. Results and Discussion

3.1. Environment-responsive Peptide Amphiphiles

Peptide amphiphiles can be modified by changing the secondary structure to mediate cell penetration and respond to either the tumor microenvironment or tumor-specific enzymes for controlling drug release [11-13]. Cancer condition has been linked to a lower pH and higher temperature environment due to a fast metabolism, which provides a good physical target for controlled drug release. For example, the self-assembled structure of pH-sensitive peptide amphiphiles could be changed to ensure controlled release of the drugs. Stupp et al. encapsulated Camptothecin (CPT) with incorporation of oligo-histidine H6 sequence. Two PAs that self-assembled into either nanofibers or spherical micelles were designed by incorporation of the aliphatic tail to the N-terminus or next on the C-terminus, respectively. Results showed that up to 60% of CPT drugs could be encapsulated by PAs nanofibers. Upon changes in pH from 7.4 to 6 and protonation of histidine residues, the two nanostructures would be broken, resulting in the desired drug release of CPT in the cancer site [14]. Fu and colleagues loaded selenium nanoparticles with doxorubicin conjugated with RGD peptide for enhancing cellular uptake and anti angiogenic activities. After internalization of the conjugated nanoparticles into the cell, drugs can be triggered to release under exposure to acidic conditions in lysosomes. The results suggest an anti-angiogenesis effect of the peptide nanosystem-drug conjugate on MCF-7 tumor cells. This is due to the down regulation of the VEGF-VEGFR2 signaling pathway causing apoptosis and cell-cycle arrest in endothelial cells [15]. Zhao et al. designed a pH-responsive peptide amphiphile in which the apparent pK_b of peptide is very close to the pH tumor microenvironment. The protonation of amphiphilic peptides at a weakly acidic pH trigger disassembly in the tumor microenvironment [16].

The self-assembly or disassembly of PAs could be initiated by the incorporation of a functional group responsive to enzymes. Proteases (e.g. α -chymotrypsin) and phosphatases are the main enzymes that have been used for the construction of peptide amphiphiles self-assembly. Assembly and disassembly of "KRRASVAGK[C₁₂]-NH₂" by enzyme-driven process showed that the self-assembly of PA upon exposure to the enzyme protein kinase causes phosphorylation which give rise to disassembly [17]. Upon treatment with alkaline phosphatase, the fibers start reassembly. The KLD12 peptide

(Ac-KLDLKLKLDL) with alternating hydrophobic and ionic hydrophilic amino acid residues, form established β -sheet hydrogel structures in aqueous solutions [18]. The sequence of KLD12 peptide is sensitive to protease and contains a protease-cleavable region in the self-assembling motif. Self-assembled peptide allows the release of therapeutics while interacting with disease-associated proteases [19]. The enzyme-cleavable linkers GFLG oligopeptides was used to bind the doxorubicin to the terminal of mPegylated dendron which self-assemble into nanoparticles. The drug release assay demonstrates that doxorubicin quickly is released from the conjugated systems as soon as the nanoparticles are taken up by tumor cells. The conjugated formulation demonstrated increased antitumor efficacy and biosafety in comparison with the free doxorubicin. This is attributed to the synergistic effects of peptide dendron, nanoscale materials and enzyme-sensitive linker [20]. The self-assembly of peptide-amphiphile immobilized on the mesoporous silica nanoparticles (MSNs) was used to assemble a nanovalve for a novel drug delivery. Nanovalves contain two main parts including a hydrophobic alkyl chain and a hydrophilic sequence of amino acid. The hydrophilic part contains a Tat48-60 peptide sequence and an RGDS targeting ligand. Antitumor drug doxorubicin was entrapped in the pores of MSNs. Experiments show that Tat48-60 peptide could increase intercellular drug release and RGDS peptide assist the active targeting of doxorubicin to integrin $\alpha v \beta 3$ positive tumor cells. High concentration of glutathione (GSH) in cytosol triggered drug release which reveals a noticeable toxicity to tumor cells [21].

3.2. Targeting the Surface of Tumors by Peptide Amphiphiles

The reports have shown that peptide amphiphiles can be designed in such a way that binds with high affinity to specific cell surface receptors. An excellent approach to increase the accumulation of therapeutic agents inside tumor tissues supposed to be functionalization with tumor-targeting motifs. Excellent biological functionality of various sequences of peptide amphiphiles makes them an excellent candidate to specifically bind to a range of overexpressed tumor associated receptors [11]. Integration of targeting ligands with the peptide amphiphiles leads to a prolonged structural stability through resistance to proteolytic degradation. Reports show that incorporation of liposomes with melanoma targeting peptide-amphiphile ligand was stable due to the protection of peptide-amphiphile triple-helical structure [22]. Folate receptor is overexpressed in several tumor types which can be exploited to deliver therapeutic compounds directly to cancer cells. The alginate-peptide amphiphile core-shell conjugated to doxorubicin was used to target the folate receptors. A shell of peptide amphiphile nanofibres covers doxorubicin-conjugated alginate. The combination effect of the spherical geometry of the core and the fibrous shell formed by self-assembly of peptide amphiphiles offer high drug loading per surface area and high surface to volume ratio respectively which result in a suitable model for drug target

delivery. The results showed that the designing microparticles have 60 times greater cytotoxicity in comparison with non-targeting particles [23]. The other study developed a PAs that activates the FGF-2 receptor and drive peptide amphiphiles self-assemble into supramolecular nanoribbons. These results highlight specific activation of the FGF-2 signaling pathway by the FGF2-PA nanoribbons and its potential application in the encapsulation and delivery of the native FGF-2 protein [24]. Integrins play an important role in cell proliferation, migration, invasion and survival being the

major attractive target for drug delivery among many receptor molecules known to be overexpressed in tumor cells [25]. The cell adhesive sequence of a great number of extracellular matrices such as blood and cell surface proteins is the tripeptide RGD and almost most integrins recognize this sequence [26, 27]. Tumor vasculature expression of $\alpha\beta3$ and $\alpha\beta5$ integrins could be selectively targeted by RGD peptides being overexpressed specifically in the tumor vasculature [28].

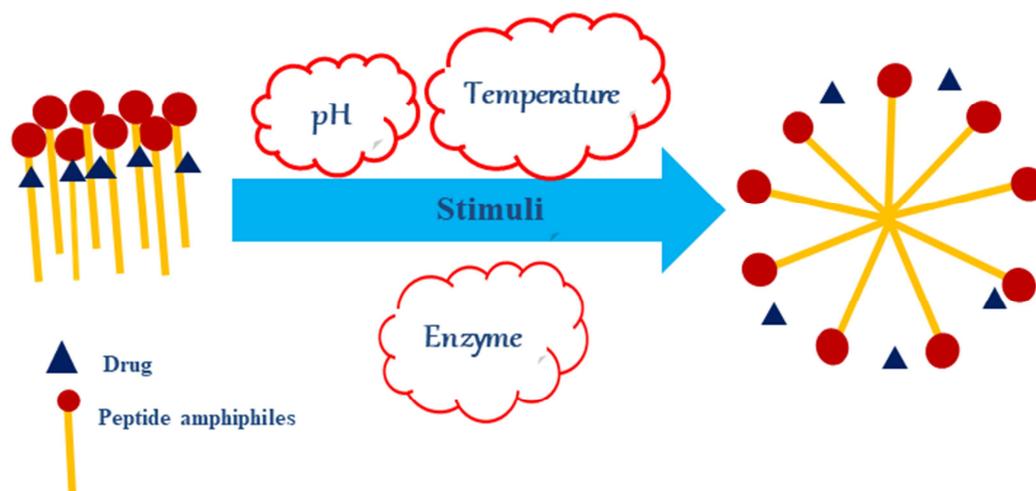


Figure 1. Shows structural change of peptide amphiphiles in response to physiological stimuli.

3.3. Combination Therapy

Lu et al [29], reported the use of cationic membrane lytic peptide amphiphiles (PAH6) to carry doxorubicin (Dox) which is inserted in an ATP-binding aptamer-incorporated DNA scaffold. Peptide amphiphiles of PAH6 with therapeutic agent properties comprises a polyhistidine part for the “proton sponge” effect, a cationic lytic structure, and an alkyl chain to drive the self-assembly. Dox-loaded DNA with PAH6 formed a spherical nanocomplex with particle sizes lower than 100 nm. The results of the study showed that the PAH6 peptide kills cancer cells via rapid membrane disruption and depolarization. In brief, the Dox-DNA/PAH6 nanocomplex displayed considerably enhanced therapeutic efficacy with a reasonable selectivity for cancer cells. Studies showed that combination therapy of cell penetrating peptide and receptor-targeted protein such as transferrin can improve the transfer of small molecules to brain compared to the system that only use receptor-targeting [30]. One promising pH-responsive cell penetrating peptide is TH (AGYLLGHINLHHLAHL [Aib] HHIL-NH₂) in which all lysines in the TK (AGYLLGKINLKKLAKL [Aib] LLIL-NH₂) sequence are substituted by histidine. There was no cellular uptake of TH peptide either in normal tissue or in blood circulation due to the neutral pH environments. However, the cell-penetrating efficiency of TH is activated in a low-pH environment of tumor. This is attributed to the protonation of histidine in TH peptides that could change the negative surface charge of the TH peptide to positive. Reports

show that loading Paclitaxel with TH-modified liposomes exhibited more significant tumor growth inhibition than free Paclitaxel at lower pH as compared to physiological pH both in vivo and in vitro [31].

4. Conclusion and Future Perspective

The development of peptide amphiphiles in response to tumor microenvironment or tumor-specific enzymes are the promising trend which allows development of targeting therapy with high efficiency. Self-assembled peptide amphiphiles can be manipulated into stable and well-defined nanostructures including tubes, vesicles, and hydrogels, and each is appropriate for delivery of specific types of anticancer drugs. There is evidence that engineering peptide amphiphiles nanostructures could provide multiple functions including cell penetration, specific targeting and stimuli-responsive drug delivery systems. However, most of the peptide-drug conjugates can only respond to a *single stimulus and are not able to overcome multiple* biological barriers before it reaches its target *site*. A *synergistic* form of multidisciplinary research areas including chemistry, biomaterials, surface engineering, and nanomaterials in addition to recent understanding of tumor biology may allow tailoring drug delivery systems based on the *targeting characteristics*. It needs for a broader perspective on *solutions to solve* the problems created by *barriers*.

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