MINIREVIEW

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Peptide-based nanomaterials for gene therapy

Wei Zhang,[a] Qing Chen,[a] Feng Wu,[a] Jun Dai, [iD] [b] Defang Ding,*[a] Jun Wu, [iD] *[a] Xiaoding Lou [iD] [a] and Fan Xia [iD] [a]

Gene therapy is a novel therapeutic method and widely used for treating numerous diseases. However, the utilization of suitable materials for specifically and effectively delivering therapeutic oligonucleotides (ODNs) into a targeted site remains a great challenge. Regarding this, by possessing the capabilities of high loading rate, good stability, targeting ability and biological barrier penetration, peptide-based nanomaterials are developing rapidly and becoming a new trend in the application of gene therapy. In this review, a variety of peptide-based nanomaterials designed for gene therapy are briefly demonstrated, focusing on their main constituents in terms of three aspects: (1) small molecules, (2) nanoparticles and (3) polymers. Using peptide-based nanomaterials, a controlled gene delivery process can be achieved and directly monitored in a real-time mode. In future work, different designs of peptide-based nanomaterials need to be explored for higher gene transfection efficiency and a better therapeutic effect. In the end, some challenges and deficiencies are mentioned for bringing more attention to accelerate the research of peptide-based nanomaterials.

1 Introduction

In recent decades, gene therapy enjoyed growing interest in the field of clinical disease treatment.[1-6] However, because of being easily subjected to degradation and poor cellular targeting and endosome escaping abilities, direct utilization of naked therapeutic ODNs as drugs was gradually avoided.[5,7,8] Hence, establishing a system of selectively delivering therapeutic ODNs into targeted cells in pursuit of an effective disease therapy has drawn extensive attention.[9-11]

Peptides, composed of amino acid monomers with amide bonds,[12,13] are recognized as one group of the fundamental units to construct numerous bio-nanomaterials for applications including gene therapy.[14-22] By possessing different R groups, amino acids have their individual structure and function.[23,24] Currently, there are twenty natural amino acids and a large number of nonstandard amino acids. The combination and arrangement of different amino acids are highly diversified and varied, making the peptides rich in a variety of capabilities,[25] such as tissue targeting,[26-28] membrane penetration,[29-33] endosome escaping[34-37] and nuclear localization.[38-40] Moreover, functional components including luminogens and polymers are widely used to conjugate with peptides, resulting in a variety of peptide-based nanomaterials.[41-47] Compared with peptides without functional components, peptide-based nanomaterials

can provide more therapeutic applications.[48-52] For example, to achieve a high loading rate of drugs and better stability *in vivo*, the effective method is to introduce biopolymers. Herein, peptide-based nanomaterials have been largely enriched by linking with different components, which ensured specificity and selectivity and conferred satisfactory functions of gene therapy.[53-58]

Numerous significant studies of peptide-based nanomaterials for the purpose of gene therapy have been published recently. In this vein, we review several recent studies on peptide-based nanomaterials (Fig. 1) consisting of three different functional components including (1) small molecules, (2) nanoparticles, and (3) polymers, and focus on the design strategy for gene therapy. Finally, the difficulties and challenges

[a]Engineering Research Center of Nano-Geomaterials of Ministry of Education, Faculty of Materials Science and Chemistry, China University of Geosciences, Wuhan 430074, China. E-mail: dingdf@cug.edu.cn; junwu@cug.edu.cn

[b]Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430074, China

Fig. 1 Scheme of peptide-based nanomaterials for gene therapy.

of using peptide-based nanomaterials for gene therapy would be discussed, and a brief perspective of future tasks in this field is pointed out.

2 Function of peptides

We have summarized some functional peptides as shown in Table 1.

3 Peptide-based nanomaterials combined with different molecules for gene therapy

3.1 Small molecules

Small molecules can easily diffuse through the cell membrane and reach the target site. And some small molecules such as fluorescent molecules[86-91] and positively charged peptides[92-94] are able to combine with negatively charged nucleic acids stably, thus improving the loading capacity, the targeting ability and the transfection efficiency of peptide-based nanomaterials and enabling the materials to be imaged in real-time. In recent decades, traditional fluorescent molecules have been studied widely, but their emissions could be weakened at high concentrations because of the aggregation-caused quenching (ACQ) effect.[95,96] In 2001, Tang and his colleagues proposed the concept of aggregation-induced emission (AIE) to illustrate a series of fluorescent molecules that emit strong fluorescence in the highly aggregated state.[97] Different from the case of fluorescent molecules affected by the ACQ effect, for AIE luminogens (AIEgens) there is no need to control their concentration during use and they can emit fluorescence in the aggregated state, and some AIEgens have photosensitivity, so they are widely used in bioimaging,[98-101] biosensing[102,103] and the field of biological therapy.[104-109] Our group have reviewed some applications of AIE-based materials.[110-112]

The covalent binding of AIEgens and peptides allows not only the biological functions of peptides but also the aggregation luminescence properties of AIEgens, which helps deliver gene therapy drugs. Our group developed self-assembled nanoparticles named TNCP/ASO-NPs (Fig. 2a), which could efficiently deliver antisense single-stranded DNA oligonucleotides (ASO) to the targeted cells.[113] TNCP/ASO-NPs self-assembled from a peptide-conjugated AIEgen (TNCP) and ASO. The amphiphilic TNCP consisted of the hydrophobic AIEgen PyTPE and a peptide sequence which contained three parts: (1) a peptide (DGR or RGD) that helped TNCP/ASO-NPs to target integrin $\alpha_v\beta_3$; (2) a nuclear localization sequence (KRRRR) that assisted ASO to enter the nucleus through nuclear pore complexes; and (3) a CPP (RRRR) that assisted nanoparticles to enter the cell and escape from endosomes. As the hydrophobic core, the PyTPE promoted the self-assembly of TNCP/ASO-NPs into nanoparticles, mainly distributed between 76 and 198 nm (Fig. 2b). TNCP/ASO-NPs selectively bound to integrin $\alpha_v\beta_3$ and rapidly entered the cytoplasm, then partially released ASO in the cytoplasm to produce intracytoplasmic interference. What's more, TNCP/ASO-NPs selectively combined with importin and transported into the nucleus, then released most of the ASO in the nucleus to produce endonuclear interference. Within 5 minutes, PyTPE showed yellow fluorescence on the cell membrane, lasting more than 150 minutes, showing good real-time imaging characteristics. The correlation coefficient of TNCP and ASO-Cy5 and the confocal laser scanning microscopy (CLSM) and the biological electron microscopy (bio-TEM) cell images suggested that TNCP/ASO-NPs were delivered into overexpressed integrin $\alpha_v\beta_3$ cells effectively and disassembled effectively. *In vivo* experiments of tumor-bearing mice and western blot assays of tumor tissue showed that ASO was delivered into tumor tissues and it inhibited tumor growth by inhibiting Bcl-2 expression (Fig. 2c). By combining AIE with peptides and self-assembling with ASO, TNCP/ASO-NPs have

Table 1 Functional peptides

Type	Sequence	Function	Ref.
Targeting peptides	ASSLNIA	Treating heart and skeletal muscle	59
	DDDDDD	Targeting hard tissue (bone and teeth)	60
	RGD	Targeting multiple integrin overexpression tumor cells	61–63
	KCCYSL	Targeting HER2-positive tumor cells	64 and 65
	(KLAKLAK)$_2$	Targeted destruction of the mitochondrial membrane	66–69
Cell-penetrating peptides (CPPs)	RKKRQRRR	Penetrating the cell membrane	29 and 70
	R$_9$	Penetrating the cell membrane	71 and 72
	CRGDKGPDC	Penetrating the cell membrane	72
Endosomal escape peptides	GLFGAIAGFIENGWEGMIDG	Destructing the membrane of endosomes	73
	WEAALAEAALEAALEAALEAALEAALAALA	Destructing the membrane of endosomes	74
Nuclear localization signal (NLS) peptides	PKKKRKV	Providing intranuclear transport	75 and 76
	GYGPKKKRKVGGC	Providing intranuclear transport	77
	KRRRR	Nucleocytoplasmic trafficking	78 and 79
Responsive peptides	PLGVR, LGLAG	Responsive to metalloproteinase-2 (MMP-2)	67 and 80–82
	DEVD	Responsive to caspase-3	83 and 84
	GFLG	Responsive to cathepsin B (CB)	85

Fig. 2 (a) Structure and function of TNCP and TNCP/ASO-NPs. (b) Transmission electron microscopy (TEM) images of $T_D NCP$ and $T_D NCP/ASO$-NPs, scale bars: 200 nm. (c) Western blot of MDA-MB-231 cells incubated with different gene therapeutic agents. Reproduced with permission.[113] Copyright 2019 Wiley-VCH. (d) Self-assembly of the FC_{siRNA}−PyTPA complex and schematic of cellular uptake and inhibition of Bcl-2 expression. (e) TEM images of FC_{siRNA}−PyTPA and FC_{siRNA}−PyTPA incubated with CB. (f) Relative volume changes (V/V_0) and body weight change of tumors in each group during treatment. Reproduced with permission.[114] Copyright 2020 Wiley-VCH.

significant specific nuclear imaging functions and tumor treatment effects, confirming the important role of small molecules in the imaging and structural self-assembly of peptide-based nanomaterials used for gene therapy.

Recently, in order to further study peptide-conjugated AIEgen nanomaterials for gene therapy, our group reported a multiple-agent-therapy probe (MATP) named FC_{siRNA}−PyTPA (Fig. 2d).[114] FC_{siRNA}−PyTPA was self-assembled from peptide-based molecular FC-PyTPA and siRNA, where FC-PyTPA was synthesized by conjugating small molecules C_{16} and AIEgen PyTPA with a short peptide. The short peptide was used to transport siRNA and respond to the tumor microenvironment, the amphiphilic structure with C_{16} and GGGH could self-assemble to form nanofibers and kill cancer cells and the AIEgen PyTPA was used for image-guided photodynamic therapy (PDT). When FC_{siRNA}−PyTPA reached the tumor site, MMP-2 divided FC_{siRNA}−PyTPA into FC_{siRNA} and PyTPA, which were internalized by macropinocytosis and caveolae-mediated endocytosis, respectively. Then, FC_{siRNA} entered the cells and self-assembled into nanofibers to destroy the structure of lysosomes through the reaction

of CB, which was highly expressed in lysosomes. siRNA escaped from the lysosomes and silenced the gene. At the same time, we applied light at the right time to give the PDT effect of PyTPA full play. According to TEM (Fig. 2e), FC_{siRNA} self-assembled into nanoparticles, then transformed into nanofibers under the action of CB to destroy lysosomes as shown in bio-TEM. The CLSM and absorption spectra suggested good imaging characteristics and PDT activity of PyTPA. The co-localization experiment and western blot assay indicated that siRNA was carried into the cell, where it successfully escaped from lysosomes and down-regulated the expression of Bcl-2 to promote cancer cell death. Finally, the triple combination therapy successfully down-regulated the expression of anti-apoptotic proteins and effectively inhibited tumor growth (Fig. 2f). This work showed us that by combining small molecules with functional peptides, siRNA can be effectively transported, and also proved the important role of peptide-based nanomaterials in gene therapy and multiple therapy.

There are also other small molecules used in peptide-based nanomaterials to promote structural self-assembly and for

gene therapy. For example, Kostarelos and his co-workers[53] designed self-assembled peptide nanofibers (PNFs) composed of palmitoyl and a peptide (GGGAAAKRK), which could deliver siRNA and silence the target Bcl-2 in specific loci of the brain. Liu and co-workers[115] combined a stearyl segment that self-assembled inside the structure in an aqueous environment with peptide to construct an α-helical structure and promote hydrophobic interactions with the cell membrane, which led to the improvement of gene transfection efficiency.

3.2 Nanoparticles

Nanoparticles such as gold nanoparticles (AuNPs), nano-diamonds (NDs), and porous silicon nanoparticles are widely studied because of their special physical and chemical properties, such as easy surface functionalization, good stability and easy size control, so they are often used in the field of gene therapy.[116–118] When a peptide is combined with nanoparticles, it can improve the targeting ability of nanomaterials, reduce the biological toxicity and improve the therapeutic effect.

AuNPs are some of the promising nanoparticles as they are nontoxic and can be easily modified on the surface or a good single nanoparticle carrier.[119–121] As gold has been approved by the FDA for preclinical trials, gene modification of rat mesenchymal stem cells (rMSC) with AuNPs is expected to generate therapeutic cell lines. Strouse and co-workers[122] designed a solid gold nanoparticle AuNP-complex for delivering genes into mesenchymal stem cells (MSC) (Fig. 3a). The surface of AuNPs was modified with a BDNF/mCherry fusion gene (6.6 kbp), which could express the BDNF/mCherry fusion protein, and a Ku70 peptide whose N-terminal was modified with

cysteine through thiol linkage chemistry to form the AuNP-complex of about 130 nm (Fig. 3b). The Ku70 peptide is an intriguing pentapeptide from Ku70 which is a DNA repair binding sequence and plays a role in antiapoptosis. What's more, the N-terminal cysteine modified Ku70 peptide is zwitterionic and reduces electrostatic interactions between the BDNF/mCherry fusion gene and AuNP peptide surface which is effective for improving nanoparticle's gene transfection. According to the calculated loading level of the peptide per AuNP, a value of 3.6 ligands per nm^2 was obtained. The optical images showed that more than 80% of rMSC cells expressed after transfection with the AuNP-complex within 4 days, and a Cedex Cell Counter and analyzer system showed that 98.3% of rMSC cells survived after single transfection, which indicated that the gene transfection of MSC population was successfully achieved by using the AuNP-complex with no significant effects on downstream of the MSCs. And the western blot analysis showed that the expression of BDNF protein was time-dependent in the media after gene transfection (Fig. 3c). This study established a new method to transfect the BDNF/mCherry fusion gene and proved that AuNPs modified by a gene and Ku70 peptide can effectively change the protein expression of MSCs and induce one-step transformation of rMSCs, while avoiding an apoptotic response.

The NDs are attractive because of their long-term particle tracking *in vivo* and fluorescence cell labelling/imaging *in vitro* with no inflammatory indications and no immune response in animal models.[123–125] Lo and co-workers[126] reported cationic peptide-functionalized NDs to enhance cellular uptake and deliver loaded antisense ODNs to the nucleus (Fig. 3d). The 30 nm NDs were modified with dual-function, cationic TAT-NLS
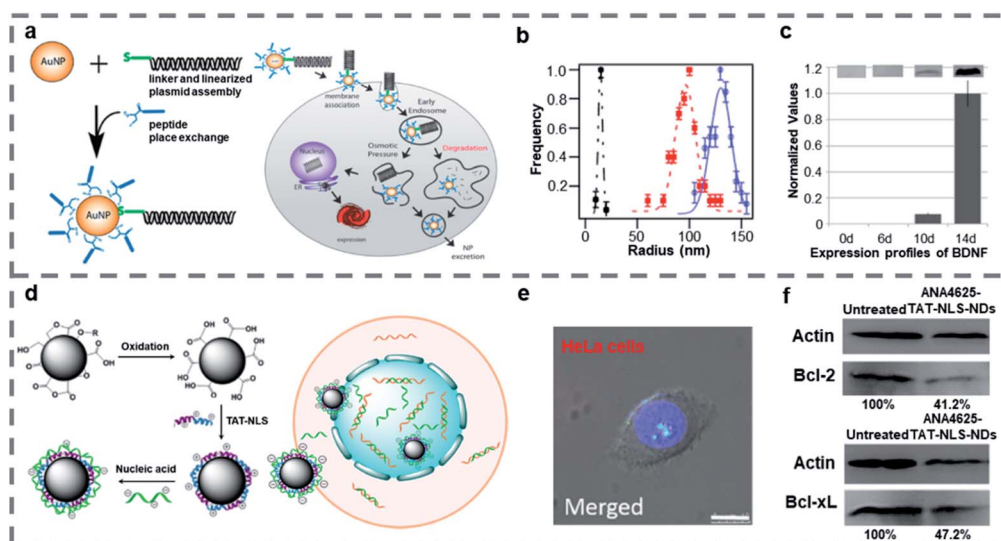

Fig. 3 (a) Assembly of the AuNP-complex, the fusion gene and schematic of cellular uptake of the AuNP-complex and subsequent exogenous BDNF/mCherry protein expression. (b) Dynamic light scattering data for the AuNP-gene (blue, 130 nm), the linearized gene (red, 97 nm), and 6.6 nm water-soluble BSPP-AuNPs (black, 15 nm). (c) Time-dependent secretion levels for BDNF expression determined using western blot analysis. Reproduced with permission.[122] Copyright 2014 American Chemical Society. (d) Synthetic scheme of TAT-NLS-NDs and cargo-loaded TAT-NLS-NDs and schematic of cargo-loaded TAT-NLS-NDs entering cells and nucleus. (e) CLSM of ANA4625-Cy3-TAT-NLS-NDs (red) in HeLa cells stained with Hoechst (blue), scale bar: 10 μm. (f) Western blot analysis of Bcl-2 and Bcl-xL expressions in MCF-7 cells after treatment with or without ANA4625-TAT-NLS NDs. Reproduced with permission.[126] Copyright 2018 American Chemical Society.

peptides in aqueous media, then the nucleic acid ANA4625 was loaded by electrostatic interaction. The TAT-NLS was formed from HIV TAT protein and SV40 large T protein NLS, which could improve the efficiency of gene transfection and expression. And the ANA4625 could reduce Bcl-2 and Bcl-xL gene expression in lung carcinoma cells. Wide-field optical imaging showed that the ANA4625 was delivered into the cells by TAT-NLS-NDs more effectively than by carboxyl-NDs, and CLSM showed that only TAT-NLS-NDs with smaller size could enter the nucleus without aggregation (Fig. 3e). Thiazolyl blue tetrazolium bromide (MTT) assay and western blot analysis (Fig. 3f) indicated that ANA4625 carried by TAT-NLS-NDs exhibited high cytotoxicity in MCF-7 cells by inhibiting the Bcl-2 and Bcl-xL gene expression. Compared to uncoated NDs, the TAT-NLS-NDs were confirmed as a more efficient carrier, which promoted the cellular uptake and delivered the nucleic acid into the nucleus with low cytotoxicity.

There are many other nanoparticles used in gene therapy. For example, Sailor and co-workers[127] reported porous silicon nanoparticles combined with fusogenic liposomes and the outer sheath of homing peptides to selectively target macrophages and transfect an ODN into the cytosol. Langel and co-workers[128] developed a new platform for transfecting plasmid (pGL3), SCO and siRNA by using magnetic nanoparticles (MNPs, Fe_3O_4) and CPPs.

3.3 Polymers

Polymers can form a stable complex with a gene and have the characteristics of high safety, low immunogenicity and easy structure modification.[129,130] In gene therapy, cationic polymers and hydrophilic polymers are widely used. Cationic polymers such as PEI and chitosan can compress DNA and avoid degradation by lysosomes.[131,132] Hydrophilic polymers such as PEO and PEG can improve the water solubility and stability of the materials.[133,134] When the polymers are combined with peptides,

the targeting property, stability and gene transfection efficiency of the materials can be improved.

Some peptides are hydrophobic and easily precipitate and aggregate *in vivo*. When peptides combine with hydrophilic polymers, they can form a self-assembly structure, which increases the hydrophilicity, the *in vivo* stability of the materials and contributes to the uptake by target cells.[135–138] Leong and co-workers[139] reported PEGylated nanoparticles (P-HNPs) (Fig. 4a) self-assembled from the cationic α-helical peptide named PPABLG for delivering Cas9 expression plasmid with sgRNA. The traditional CPPs either were too small to penetrate the cell membrane or lacked an adequate cationic charge density, which made CPPs unable to be used as an independent gene vector. However, PPABLG could bind and concentrate short siRNA and plasmid DNA while maintaining high membrane-penetrating ability for enhancing the ability of cellular internalization and endosomal escape. In order to enhance the extracellular stability and the potential applications *in vivo*, the PPABLG-Cas9 expression plasmid and sgRNA complexes (HNPs) were modified using PEG-polythymine_{40} (PEG-T40) in the formulation without changing the size of the nanoparticles (Fig. 4b). By studying the internalization pathway of P-HNPs, it was found that the internalization of P-HNPs was related to the clathrin-mediated pathway, macropinocytosis and caveolae-mediated uptake. The colloidal stable-HNPs achieved up to 60% Cas9 transfection efficiency and 67.4% sgRNA uptake efficiency. *In vitro*, P-HNPs were used to deliver Cas9 expression plasmids and Plk1-targeting sgRNAs into HeLa cells, resulting in obvious inhibition at the target site and causing cell apoptosis by 46.2%. Experiments *in vivo* and western blot analysis (Fig. 4c) confirmed that P-HNP_{PCas9+sgPlk1} led to a tumor suppression of >71% and decreased the expression level of Plk1 protein by 67%.

Platinum is a widely used chemotherapy drug to treat a variety of cancers.[140,141] And various polymeric nanomaterials
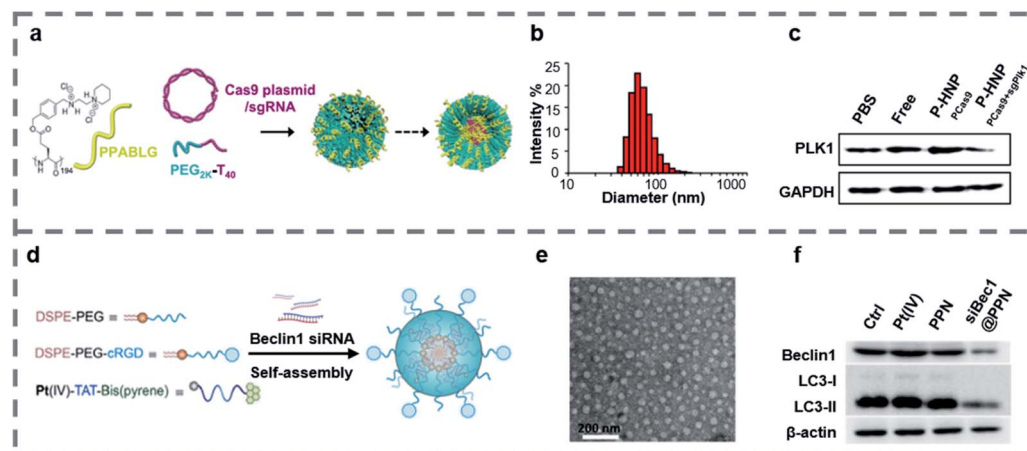

Fig. 4 (a) Schematic illustration showing the formation of P-HNPs and the intracellular activity of Cas9 expression plasmid/sgRNA in performing genome editing or gene activation. (b) Size of P-HNPs formed from PPABLG : px458 : PEG2K-T40 at a ratio of 30 : 1 : 1. (c) The expression level of Plk1 protein in tumor tissues. Reproduced with permission.[139] Copyright 2018 the author(s) published by PNAS. (d) Illustration of the self-assembled nanoprodrug system. (e) TEM images of siBec1@PPN. (f) Western blot of Beclin1 and LC3-II in Pt-resistant A549 tumor cells treated with PBS (Ctrl), Pt(IV), PPN, and siBec1@PPN. Reproduced with permission.[145] Copyright 2019 American Chemical Society.

were designed to deliver cisplatin, which improved the effects of the circulation *in vivo* of cisplatin.[142,143] What's more, inhibition of autophagy may reduce the resistance of tumor cells to cisplatin.[144] Wang and co-workers[145] developed a self-assembled nanoprodrug platform named siBec1@PPN containing cisplatin and Beclin1 RNAi (siBec1 is an autophagy initiation factor), which could inhibit the growth of the cisplatin-resistant tumor. The nanoprodrug platform was self-assembled using three parts including Pt(IV)-peptide-bis(pyrene), DSPE-PEG and cRGD-modified DSPE-PEG (Fig. 4d). The Pt(IV)-peptide-bis(pyrene) loaded Pt(IV) with a load rate up to 95%, released Pt(II) in the presence of glutathione (GSH) and delivered siBec1 into the cytoplasm, which inhibited autophagy and increased the cell apoptosis. The DSPE-PEG increased the stability and biocompatibility of the nanoparticles and the cRGD helped nanoparticles to target the tumor cells. As TEM images (Fig. 4e) show, the siBec1@PPN is a spherical structure with a size of 54.44 ± 11.13 nm. What's more, the western blot (Fig. 4f) showed that the siBec1 was transfected successfully and it inhibited the Beclin1 expression on A549 tumor cells. Animal study results showed that the siBec1@PPN reversed Pt resistance by siBec1-mediated autophagy inhibition and the tumor cells were apoptotic. Overall, siBec1@PPN showed us the ability of peptide–polymer complexes to transfer genes effectively and inhibit the growth of tumor cells.

Due to the excellent properties of polymers, a large number of studies have been carried out. For example, Rosenecker and co-workers[146] developed compact and monodisperse peptide-poloxamine nanoparticles, which could long-term repair the cystic fibrosis transmembrane conductance regulator defect *in vitro* and *in vivo* with a safe profile. Wang and co-workers[147] reported that polyurethane nanomicelles modified by an osteoblast-targeting peptide could selectively target osteoblasts to deliver siRNA/microRNA without overt toxicity or causing an immune response *in vivo*.

4 Conclusions

In this review, several peptide-based nanomaterials self-assembled from peptides and three individual functional components are introduced for the application of gene therapy. Compared with pure peptide sequences, peptide-based nanomaterials with other functional components appear to be more ideal gene delivery materials by taking advantage of multifunctionality, good biocompatibility, high load rate *etc.* In order to improve the specific targeting and transfection efficiency for gene therapy and add additional features to the design, more details but not limited to the following issues need to be considered: (1) the design of small molecule–peptide nanomaterials requires rational selection of suitable functional polypeptides and small molecules, in terms of the length, electrical properties, hydrophilicity and hydrophobicity of peptides and structures of small molecules, to avoid the interference between peptides and small molecules; (2) there is room for improvement of preparation of nanoparticle–peptide nanomaterials to enhance the homogeneity of products and reduce the side effects *in vivo*; (3) the non-specific adsorption of

polymers could be further eliminated, and accelerating the targeting of polymer–peptide nanomaterials to tumor cells would be more favored; (4) the design strategy of peptide-based materials such as the load part of ODNs, biological functional peptides, the ratio of peptides and other components and the self-assembly structure should be considered. However, peptide-based nanomaterials used in gene therapy still have some problems such as poor structural stability in serum, being easily degraded *in vivo* and low gene loading rate. What's more, the combination of peptides with other components without affecting the function of each part is still a problem to be solved. In the future, it is necessary to study the secondary structure of peptides in depth and to improve the circulation time *in vivo* and the accumulation of peptide-based nanomaterials in the target tissue for clinical use. And the applications of peptide-based nanomaterials in other fields, such as cancer treatment, bioimaging, and tissue biomaterial engineering, need to be further studied.

On the basis of notable achievements, peptide-based nanomaterials will be developed with more novel and efficient designs in the near future. In order to obtain advanced functional peptide-based nanomaterials, for example, it is necessary to explore the complex structure of peptides containing unnatural amino acids and optimize multifunctional components to ensure their precise functions. Because of the space limitation, this review is confined to three components (small molecules, nanoparticles, and polymers) which construct peptide-based nanomaterials. However, we hope that it will be able to promote the research of peptide-based nanomaterials for gene therapy and accelerate their development in the fields of nanomaterials, biology and chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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