Functionalized Peptides in Nanomedicine for Effective Cancer Therapy

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Peptide-functionalized nanomedicine, which addresses the challenges of specificity and efficacy in drug delivery, is emerging as a pivotal approach for cancer therapy. Globally, cancer remains a leading cause of mortality, and conventional treatments, such as chemotherapy, often lack precision and cause adverse effects. The integration of peptides into nanomedicine offers a promising solution for enhancing the targeting and delivery of therapeutic agents.

Keywords: cancer therapy ; functionalization ; nanomedicine ; nanoparticle ; peptide

1. Introduction

Cancer is a leading cause of death worldwide, accounting for approximately 10 million deaths in 2020 [1][2]. Cancer treatments include chemotherapy, phototherapy, radiation therapy, and surgery [3][4][5][6][7][8][9][10][11][12]. Chemotherapy is a traditional treatment for cancer and can effectively treat cancer, even at low doses [13][14][15]. However, since many cancer drugs are hydrophobic, injecting the appropriate drug concentration required for treatment is difficult, and direct drug injection often causes side effects owing to non-specific effects on cancer and normal cells [16][17][18][19]. Additionally, the injected drugs are removed by the reticuloendothelial system (RES), and only a small fraction of the drug is delivered to the cancer cells, making it difficult to reach a sufficient concentration for treatment [20][21][22][23][24]. Drug delivery systems have been developed over the past few years [25][26][27]. Mesoporous silica nanoparticles (MSNP), gold nanoparticles (GNP), quantum dots (QD), polymeric nanoparticles, and metal-organic nanoparticle frameworks (MOF) have received attention as nanomedicine platforms because they accumulate in cancer tissues owing to the enhanced permeation retention (EPR), which not only helps selective drug delivery but also allows porous particles to load the cancer drugs in their pores without specific modification [23][28][29][30][31][32][33][34][35][36]. However, these nanomaterial-based systems also have problems with biocompatibility, RES escape, controlled release of loaded drugs, and selective cancer cell targeting [37][38][39][40][41][42]. Therefore, many researchers have modified various nanomedicine substances to add new functions to cancer treatment [43][44][45][46][47].

A peptide is a short chain of amino acids, less than 50 amino acids, with two or more amino acids linked through a peptide bond [48]. Peptides provide a cancer-targeting ability to nanomedicine, reducing drug side effects and increasing treatment effectiveness. In addition, the peptide itself self-assembles and is not only used as a drug carrier that carries drugs and safely delivers them to cancer cells but also treats cancer with its self-assembly structure. Lastly, peptides facilitate the controlled drug release of nanomedicine by responding to the stimuli [49][50][51][52][53].

2. Functions of Peptides

2.1. Cancer-Targeting Ligand

Nonspecific nanomedicine accumulation poses significant challenges in cancer treatment as they can inadvertently lead to adverse side effects by accumulating in healthy cells [54][55]. Furthermore, the cell membrane acts as a biological barrier, impeding efficient drug delivery to cancer cells [56]. The barrier function of the cell membrane hinders the penetration and absorption of therapeutic agents, making it challenging to achieve the desired drug concentration in cancer cells. To address these issues, cancer-targeting or cancer-penetrating peptides have been modified on nanoparticle surfaces, which enhances nanoparticle selectivity, allowing them to specifically target cancer cells. Cancer cells possess specific surface markers that differ from those of normal cells. Peptides recognize these cancer-specific surface markers and bind to them with high affinity.

2.1.1. Receptor-Mediated Peptide

The receptor-mediated peptide has a strong affinity with the receptor present in cancer cells, allowing it to selectively target and treat cancer. Craciun et al. developed a cancer cell-targeting system by modifying decapeptides in a gold nanoparticle-based gene delivery system [57]. Polyethylenimine (PEI), which has beta-cyclodextrin (β-CD), was modified on the gold nanoparticle surface. PEI is widely used as a versatile gene carrier with high transfection efficiency and reproducibility, both in vitro and in vivo. Moreover, it has a high positive charge owing to the amino groups in its structure and forms a polyplex via electrostatic interaction with negatively charged phosphorus, which is the DNA backbone. Therefore, it effectively loads the plasmid DNA required for gene therapy. The decapeptide (WXEAAYQRFL), which has a high affinity for MCF-7 cancer cells, endows NPs with targeting properties [58]. This system not only delivers plasmid DNA to cancer cells but also protects plasmid DNA from degradation by endonucleases. To compare the delivery efficiency between specific peptide-labeled nanoparticles (AuPEI–β-CD–Pep NPs) and unlabeled nanoparticles (AuPEI–β-CD NPs), in vitro transfection efficiency was evaluated in two cancer cell lines, HeLa and MCF-7, using pCS2+MT-Luc DNA as a reporter gene. In the result, AuPEI–β-CD–Pep NPs show higher and similar transfection efficiency than AuPEI–β-CD NPs in MCF-7 and HeLa cells, respectively. These results indicate that the peptide specifically interacted with MCF-7 cells and effectively delivered the loaded DNA. The modifications of decapeptides have enhanced the targeting capabilities of gene delivery systems based on gold nanoparticles. Moreover, systems modified with peptides showed high DNA delivery efficiency.

2.1.2. Cell Penetrating Peptide

Cell-penetrating peptides (CPP) can transport hydrophilic macromolecules into cancer cells via an energy-independent pathway. Therefore, the penetration effect of the system can be increased through CPP modification. Wang et al. developed a cancer-targeting system using polyphyllin I (PPI), isoreticular metal-organic frameworks-8 (IRMOF-8), and cell-penetrating peptides [59]. PPI, naturally active steroid saponins, are effective for treating liver, lung, and stomach cancers. However, it has low solubility in aquatic solutions and damages normal cells and other side effects owing to its nonselective distribution [60]. IRMOF-8, which has a pore diameter close to the crystal size of the drug, was selected for encapsulation to achieve effective PPI delivery and has a diameter of 143.13 ± 7.42 nm. In addition, it can be easily functionalized by hydrogen bonding with a polymer composed of PEG and a liver cancer-targeting peptide (CPP44, KRTPTMRFRYTWNPMK), and its diameter has increased to 202.97 ± 3.64 nm. CPP44 can recognize liver cancer cells through high expression of M160. The thiol group at the end of the CPP44 structure and the maleimide at the end of mPEG2000 formed a thioether bond through a thiol-Michael addition click reaction. This polymer can be modified into a PPI-loaded MOF (PEG-CPP44/PPI@IRMOF-8), which increases the circulation time and cellular uptake of MOF. The Cou6 was labeled with a system for cellular uptake experiments. HepG2, L02, A549, MGC-803, and HT-29 cells were incubated with Cou6-labeled PEG-CPP44/PPI@IRMOF-8. After incubation, significant fluorescence was observed in HepG2 cells, but not in the L02, A549, MGC-803, or HT-29 cells.

Small interfering RNA (siRNAs) are widely used in cancer treatment. However, the poor bioavailability and stability of siRNAs are the main problems in using siRNA for cancer therapy [61]. Cai et al. developed a cell-penetrating-peptide-modified MOF nanoparticle for siRNA delivery [62]. In this study, ZIF-90 was chosen as the drug delivery carrier. As ZIF-90 introduces an aldehyde group based on ZIF-8, it is more hydrophilic than ZIF-8, which can protect the loaded siRNA more effectively. Survivin siRNA and Oridonin (ORI) were loaded on ZIF-90 pores (ORI@survivin siRNA@ZIF-90) via electrostatic and π–π interactions. Survivin is a tumor-specific gene that is highly expressed and enhances apoptosis resistance in lung cancer cells [63]. Therefore, surviving siRNAs that inhibit survivin can effectively treat cancer if they co-deliver ORI, which causes cancer cell apoptosis [64]. After synthesis, PEG-drafted CPP33 (RLWMRWYSPRTRAYG), which specifically penetrates non-small-cell lung cancer A549 cells, was modified with drug-loaded ZIF-90 to obtain PEG-CP33@ORI@survivin siRNA@ZIF-90. The thiol group at the end of the CPP33 structure and the maleimide at the end of mPEG formed a thioether bond through a thiol-Michael addition click reaction. Coou6 was loaded instead of ORI or siRNA to confirm the cellular uptake of the system. A549, HepG2, HT-29, and MDA-MB-231 cells were incubated with Cou6, Cou6@ZIF-90, and PEG-CPP33@Cou6@ZIF-90. After incubation, strong fluorescence was observed in A539 cells incubated with PEG-CPP33@Cou6@ZIF-90, as confirmed by CLSM. Saline, siRNA@ZIF-90, ORI@ZIF-90, ORI@survivin siRNA@ZIF-90 and PEG-CPP33@ORI@survivin siRNA@ZIF-90 was injected in A549 tumor-bearing nude mice. The tumor size in the PEG-CPP33@ORI@survivin siRNA@ZIF-90 treatment group was substantially smaller than that in other groups due to the combined effect of siRNA and ORI. Modified CPP33 imparts lung cancer targeting capabilities to a system based on ZIF-90. ZIF-90, being more hydrophilic than ZIF-8, encapsulates hydrophilic siRNA and exhibits better protective effects due to steric hindrance.

2.2. Building Block of Self-Assembly Structure

In addition to using peptides as ligands to modify nanoparticles, they can also be utilized as drug-delivery vehicles by constructing self-assembled structures. Owing to their diverse physicochemical properties, peptides can form various

nanostructured nanoparticles, nanotubes, nanofibers, and hydrogels with advantageous properties compared to conventional non-biological materials [65][66][67]. This unique morphology of the self-assembled structure can be controlled by modifying the self-assembly parameters, such as solvent, ionic strength, concentration, pH, temperature, and noncovalent interactions between the building blocks [68]. Self-assembled peptides not only have unique characteristics of peptides, such as biocompatibility and cancer-targeting properties but can also effectively deliver drugs by loading various drugs into their structure [69][70][71]. In addition, self-assembled peptide structures can be used to treat cancer cells [72].

2.2.1. Drug Delivery Carrier

Once the peptide building blocks form a self-assembled structure, anticancer drugs can be loaded into the hydrophobic portion of the structure. Sivagnanam et al. utilized a self-assembled peptide structure as a drug delivery vehicle for cancer therapy [73]. The cationic tripeptide Boc–Arg–Trp–Phe–OME (PA1) self-assembles into spheres in aqueous solution. Each peptide sequence consisting of a PA1 peptide has a specific characteristic. The cationic amino acid Arg, which endows a net positive surface charge, strongly interacts with negatively charged cellular membranes and enhances the cellular uptake of the self-assembled structure. Trp has the highest emission maxima and a high quantum yield among aromatic amino acids, which endows the structure with fluorescent properties. The aromatic peptides, Trp and Phe, facilitate the self-assembly process by providing the π–π stacking interactions. Additionally, these aromatic peptides form a hydrophobic region in the self-assembled structure for drug loading. The critical aggregation concentration of PA1 was 0.962 mg/mL. An epithelial cell adhesion molecule (EPCAM)-directed aptamer was modified into PA1 to achieve a targeting effect [74]. The carboxylic acid group of the aptamers and the amine group of PA1 form an amide bond through the EDC reaction. Self-assembly of the aptamer-modified PA1 was initiated in a solution containing doxorubicin (Dox) to form a Dox-loaded peptide structure (PA1–Apt). To confirm its cancer-targeting effects, human cardiomyocyte cells AC16 (EPCAM-negative) and human breast carcinoma epithelial cells MCF7 (EPCAM-positive) were incubated with PA1–Apt. Higher fluorescence intensities of the PA1-based assembly and Dox were observed in the MCF7 cells than in the AC16 cells.

To identify suitable compounds that can be effectively delivered by these nanoassemblies, structure-based virtual screening of a small-molecule library was performed, and camptothecine (CPT), which binds most strongly to RDP, was selected. π–π stacking and hydrophobic interaction between RDP and CPT were observed in virtual screening, and this effect strengthens the bonding. To observe the biodistribution of RDP nanoassemblies, the fluorescent substance 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide (DiR) and DiR-labeled RDP nanoassemblies were injected in 4T1 tumor-bearing Balb/c female mice. The DiR-labeled RDP exhibited higher fluorescence than free DiR in tumors.

2.2.2. Therapeutic Peptide

The self-assembled peptide structure is used not only as a drug carrier but also to treat cancer directly. Zhou et al. developed a peptide sequence using structure-based virtual screening techniques [75]. In this study, a self-assembling D-peptide supramolecular nanomedicine (NMTP-5) targeting neuropilin-1 (NRP1) and mouse double-minute 2 (MDM2) was developed using structure-based virtual screening techniques. MDM2 is a negative regulator of p53 and transactivates the expression of target genes that mediate cell cycle arrest and apoptosis. MDM2 is overexpressed in various cancers, promotes p53 degradation, and inhibits p53 protein levels by binding to p53 [76]. Therefore, upregulating p53 levels by interfering with the MDM2–p53 interaction can effectively treat cancer cells. NRP1 is a transmembrane glycoprotein that is overexpressed in cancer cell membranes and regulates the cell penetration ability of peptide drugs. Therefore, NRP1-targeting peptide can effectively penetrate deep into tumors to treat cancers [77]. The sequence of NMTP-5 was ZFFYGWYGGMEKLLRGGRGERPPR, and the ZFFY sequence allowed the self-assembly of the peptide. The critical aggregation concentration of NMTP-5 is 36.2 μm and forms the fiber shape. To confirm cellular uptake, isothiocyanate-loaded NMTP-5 was incubated in SK-Hep-1 cells and SK-Hep-1 cells in which NRP1 was silenced by NRP1-targeting shRNA. Strong fluorescence was observed in SK-Hep-1 cells, whereas weak fluorescence due to NMTP-5 uptake was observed in NRP1-silenced cells. To investigate whether NMTP-5 inhibited the binding of endogenous MDM2 to p53 in SK-Hep-1 cells, an immunoprecipitation assay was performed. NMTP-5 inhibits the interaction between endogenous MDM2 and p53 and increases the p53 protein level in SK-Hep-1 cells.

In addition, Jeena et al. developed a self-assembly building block by modifying the peptide backbone with pyrene, and triphenylphosphonium (TPP) ligand targeting mitochondria [78]. FFYpK peptide was synthesized by adding L-tyrosine phosphate unit (Yp) and lysin to dipeptide (FF). The phosphate unit present in the peptide sequence is cleaved by the alkaline phosphatase (ALP) enzyme, which is overexpressed in cancer cells, to form FFYK [79]. FFYpK peptide N terminus forms an amide bond with the carboxylic acid present in pyrene, and the amine group present in the lysine side chain forms a secondary amine with 1-hexyl triphenylphosphonium bromide. FFYpK (Mito-FFYpK) modified with pyrene and TPP has a micellar structure and a negative surface charge. On the contrary, Mito-FFYK, in which the phosphate unit has

been removed by the ALP enzyme, has a fiber-shaped structure and a positive surface charge. Therefore, when the micellar structure of Mito-FFYpK reaches cancer cells, it is converted to Mito-FFYK by ALP present in the cancer cell, and since the building block is positive, it easily internalizes the cancer cell membrane and selectively accumulates in the mitochondria.

2.3. Stimuli-Responsive System

The premature leakage of drugs from nanocarriers during delivery to cancer cells is a major problem, leading to nonspecific drug distribution and the potential harm or death of normal cells [80][81]. This challenge can be overcome by modifying cancer-targeting ligands; however, it can also be addressed by controlling the encapsulated drug release [23][82][83]. The use of stimuli-responsive peptides in nanocarriers facilitates controlled drug release [84]. This approach not only minimizes damage to healthy cells but also increases the effectiveness of cancer therapy by ensuring that the drug is released at the site of the tumor in a controlled manner.

2.3.1. Enzyme Responsive Peptide

Peptides that are degraded or activated by specific enzymes react depending on the presence or absence of the enzyme. Therefore, a system can be developed to release drugs using peptides that react with enzymes overexpressed in cancer. Liu et al. developed a system that controls drug release by blocking the pores of MSNPs with GNPs using a ligand containing a peptide sequence [85]. A peptide substrate containing a urokinase-type plasminogen activator (uPA)-specific responsive peptide sequence (ESGRSAN), glutamic acid, and selenocysteine termini was labeled with rhodamine B [86]. This peptide substrate forms a gold selenium linkage (Au–Se) with the GNP and an amide bond with the silica nanoparticles, thereby forming a GNP-modified MSN (Au–Se@MSN). Additionally, the uPA-specific peptide constituting the ligand is cleaved by uPA, which is highly expressed in metastatic cancers. This phenomenon detaches GNPs capping the MSN pores and facilitates cancer-specific drug release. To confirm the leakage and responsive release of the cargo from Au–Se@MSNs, a release assay was conducted by loading isothiocyanate (FITC) into Au–Se@MSNs and MSN. Although 80% of FITC was released from the MSN group, the Au–Se@MSN group exhibited insignificant FITC release. After being simulated with 0.4 μg/mL uPA, the FITC cumulative release rate of the Au–Se@MSN group reached up to 60%. This suggests that the peptide sequence effectively controls the drug release via enzymatic stimuli. Au–Se@MSN loaded with resveratrol significantly inhibited tumor growth in an in vivo experiment. Se-Cys containing peptides, modified with nanomedicine through Au-Se bonds with GNP, block pores to prevent drug leakage and respond to uPA for selective drug release in cancer. This system can effectively reduce drug side effects and increase cancer treatment.

As mentioned above, peptides endow multi-functionality to nanomedicine. In peptide-based self-assembled nanomedicine, the peptide acts as a building block and causes the formation or collapse of the self-assembled structure in response to stimuli. Yang et al. developed a self-assembled structure comprising a Dox prodrug [87]. The Dox prodrug was constructed by forming an amide bond between the cathepsin B-cleavable peptide (FRRG) and Dox. This direct FRRG conjugation to Dox prevented premature drug release in normal tissues. Through hydrophobic interactions and π–π stacking, peptide-modified prodrugs self-assemble into cancer-activating Dox prodrug nanoparticles (CAP-NPs) that are specifically degraded into cytotoxic Dox molecules by cathepsin B, an enzyme overexpressed in cancer cells. To compare the cancer therapeutic effects, saline, free Dox, and CAP-NPs were injected into CT26 tumor-bearing mice. CAP-NP-treated mice showed minimal tumor growth compared with the saline- and free Dox-treated mice.

2.3.2. pH-Responsive Peptide

The natural amino acids lysine (K), arginine (R), histidine (H), and glutamic acid (E), which contain ionizable groups such as carboxyl, imidazole, primary amine, and tertiary amine, respond to pH by changing the charge of the molecule. Therefore, by introducing amino acids with ionizable groups into the peptide sequence, a system that responds to specific pH levels can be developed. Wang et al. studied a system that responds to the TME pH using a peptide-rich in H and K (KKKHHHH-Acp-LLLLLLLLGSPDRGD, where Acp stands for 6-aminocaproic acid) [88]. At pH 7.4, the peptide forms a self-assembled structure through electrostatic and hydrophobic interactions, capable of loading nucleic acid. The K sequence of the peptide becomes protonated at TME pH, gaining a positive charge, which, along with the peptide's RGD, enhances the uptake of nucleic acid into cancer cells. The H sequence of the peptide is protonated in lysosomes, which have a lower pH, increasing the peptide's positive charge. This increase in positive charge enhances the electrostatic repulsion between the peptides, triggering the release of the encapsulated nucleic acid drug. This multi-pH responsive system enables not only targeted cancer therapy but also controlled drug release.

2.3.3. Light Responsive Peptide

Peptides that respond to light can be synthesized by modifying the photoreactive protecting group on the peptide. PG reactivates the charge of the peptide via NIR two-photon photolysis, allowing rapid penetration into cancer cell membranes. Yang et al. developed a system based on a photo-sensitive peptide (PSP) modified liposome, which targets the cancer cell in response to light stimuli [89]. The sequence of the CPP is CGRRMKWKK, which does not possess inherent cancer-targeting ability. PSP is formed by a covalent bond between PG (1-(bromomethyl)-4,5-dimethoxy-2-nitrobenzene) and the amine group of the lysine side chain of CPP via an S_N2 reaction. Additionally, PSP is modified onto the liposome, which is composed of 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethyleneglycol) (DSPE-mPEG2000), through a thiol-Michael addition click reaction. The PSP-modified liposome (PSP-L) can act as a carrier for vinorelbine bitartrate (VB).

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