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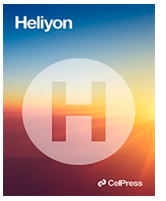

Review article

Advances in peptide-based drug delivery systems

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ABSTRACT

Drug delivery systems (DDSs) are designed to deliver drugs to their specific targets to minimize their toxic effects and improve their susceptibility to clearance during targeted transport. Peptides have high affinity, low immunogenicity, simple amino acid composition, and adjustable molecular size; therefore, most peptides can be coupled to drugs via linkers to form peptide-drug conjugates (PDCs) and act as active pro-drugs. PDCs are widely thought to be promising DDSs, given their ability to improve drug bio-compatibility and physiological stability. Peptide-based DDSs are often used to deliver therapeutic substances such as anti-cancer drugs and nucleic acid-based drugs, which not only slow the degradation rate of drugs in vivo but also ensure the drug concentration at the targeted site and prolong the half-life of drugs in vivo. This article provides an profile of the advancements and future development in functional peptide-based DDSs both domestically and internationally in recent years, in the expectation of achieving targeted drug delivery incorporating functional peptides and taking full advantage of synergistic effects.

1. Introduction

Over the past few years, drug delivery systems (DDSs) have become a research hot-spot and have been used clinically to treat various diseases, such as the polyethylene glycol (PEG)-liposome-encapsulated chemotherapy drug adriamycin (DOX) and co-polymer micelles loaded with the anticancer drug paclitaxel (PTX) [1]. DDSs can control the slow release of drugs in the body and intelligently regulate the distribution of drugs in the body in a certain time, space, and dose, further enhancing the concentration and efficacy of drugs at the therapeutic site [2–4]. DDSs are carrier systems for the targeted delivery of drugs to specific sites, which improves the stability, bio-availability, and half-life of the loaded drugs in the body. By targeting specific sites, they minimize the toxic effects of drugs on normal cells and drug degradation, help maintain a stable blood concentration balance and enhance drug enrichment at the target sites [5]. Therefore, further research and development of DDSs are necessary to improve the diagnosis and treatment of diseases, especially in oncology [6]. However, DDSs are facing limitations such as complex drug targets of action, inability to penetrate biological membranes, hydrolysis of drugs by pepsin, and the influence of the acidic tumor environment [7].

Peptide-drug conjugates (PDCs) represent DDSs generally consisting of three components (Fig. 1). The first component is the carrier, and in addition to aptamers and small molecules, organisms such as peptides, proteins, and antibodies have been intensively

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studied as carriers. The second component is the payload, which can treat relevant diseases by inducing various biological functions, mostly cytotoxic drugs or radionuclides [8]. The third component is the linker, which connects the first two components and achieves controlled drug release. Cleavable linkers also include chemically cleavable and enzymatically cleavable linkers. Chemically cleavable linkers are cleaved in organelles with acidic environments, such as lysosomes and endonucleosomes, while enzymatic cleavage linkers are cleaved by histone proteases and enzymes associated with the tumor microenvironment [9].

Peptides are the active sites and constituent fragments of enzymes, antibodies, and protein hormones and are defined by the Food and Drug Administration (FDA) as polymers consisting of ≤40 amino acid molecules [10]. Peptides have been widely utilized and developed due to their bio-compatibility, ease of synthesis and purification, high modifiability, and stability. Peptides coupled with drugs can be used in drug delivery system development and bio-pharmaceutical research, enhancing drug therapeutic strength and accuracy [11].

In peptide-constructed DDSs, peptides can be used as carriers to deliver anticancer drugs to specific sites, improving the delivery ability of DDSs with certain physiological activity and chemical modification of side chain functional groups [12], including supramolecular nanostructures such as peptide nanocarriers. Importantly, peptide carriers enhance the penetration of drugs into target cells and the specific targeting ability of drugs, effectively solving the drug delivery barrier problems. Functional peptides exhibit the ability of functional units of peptides to covalently couple with drugs under the action of linkers to form PDC systems [13]. In this paper, we expound on DDSs composed of various functional peptides in light of domestic and international research progress. This paper specifically describes the target receptors of cell-targeting peptides, the uptake pathways of cell-penetrating peptides and different environment-stimulus-responsive peptides, as well as the promising applications of DDSs consisting of these functional peptides in the clinical treatment of diseases.

2. Cell-targeted peptides

DDSs often target highly expressed receptors at the site of action, and then deliver therapeutic drugs to target cells or target tissues, which improves the therapeutic efficacy of the drugs and reduces the toxic side effects of the drugs on the organism. Among them, targeted peptides can bind specifically to the targets [14]. Cell-targeting peptides (CTPs), consisting of 3–14 amino acids, are commonly used as targeting agents. They exhibit a specific affinity for receptors highly expressed in specific cells or tissues [15], facilitating the delivery of targeted drugs to the therapeutic site. And their coupling with drugs to form DDSs has attracted significant interest. Accordingly, they are increasingly used in the treatment of oncological diseases.

Tumor homing peptides (THPs) have the ability to target tumor vascular endothelial cells and tumor cells [16,17]. THPs covalently coupled with cytotoxic drugs or supramolecular nanocarriers can form a drug delivery system to achieve targeted penetration into tumor tissues [18].

177Lu-dotatate, a PDC currently marketed for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), is formed by the growth hormone inhibitor in the homing peptide binding to the cytotoxic radiotoxicity radiotherapeutic agent 177Lu via a linker [19], which enhances affinity with the gastroenteropancreatic neurotumor cell-surface receptor and the ability to target therapy. Arap et al. [20]were the first to use tumor-homing peptides, such as RGD and NGR, to deliver DOX, and THPs-DOX couplings showed better tumor growth inhibition than DOX alone in hormonal mice. In addition, nanoliposomes encapsulated DOX and then coupled with THPs showed better anti-tumor effects. Hu et al. [21] first prepared Polyethylene glycol-poly lactic acid (PLA) nanoparticles (PEG-PLA NPs) by the coupling reaction of maleimide-thiol, and coupled the nanoparticles to THP F3 (CKDEPQRRSARLSAKPAPPKPEPKPKKPKKAPAKKK). Due to the high affinity of F3 for nucleoli expressed on glioblastoma cells, the penetration depth of F3-PEG-PLA NPs coupling encapsulated with the anticancer drug PTX was as high as 139.26 μm in a 3D multicellular glioma model, which was much higher than that of PEG-PLA NPs alone (81.02 μm). In addition, Winer et al. [22]developed F3-modified cisplatin (DDP)-polyacrylamide (PAA) coupling NPs capable of targeting angiogenic pathways in ovarian cancer. The NPs were demonstrated to almost completely inhibit tumor angiogenesis in ID8-VEGF ovarian cancer model mice by in vivo experiments, resulting in a 2.5-fold

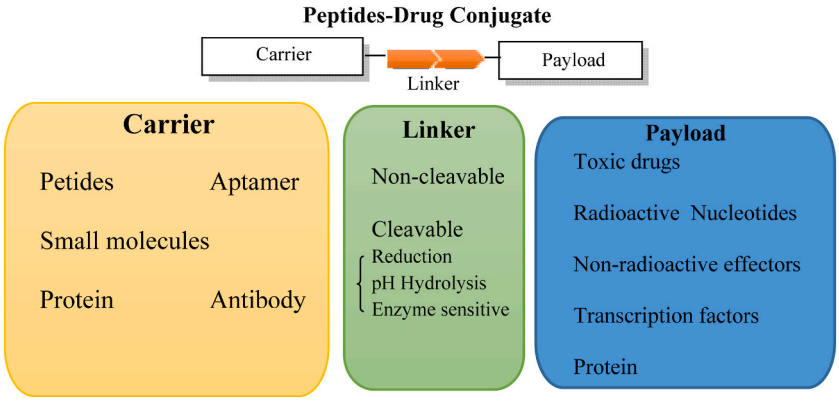

Fig. 1. Schematic structure of peptide-drug coupling, which consists of three modules: carrier, linker, and payload.

reduction in total tumor weight. In vitro experiments demonstrated that the F3-Cis-NPs were also highly bound to human ovarian cancer cells, suggesting that the tumor homing peptide-modified PAA-NPs can precisely deliver anticancer drugs to the corresponding targets and give full play to the drug efficacy, which is expected to be a biological tool for precision treatment of cancer patients.

2.1. Targeted receptors

CTPs often target drug delivery by binding to the acceptor on the malignant cells or in tumor vascular endothelial cells [23]. CTPs recognize receptor components such as integrin receptors, aminopeptidase-N (APN) (CD13), and epidermal growth factor receptor (EGFR) (Fig. 2) [24,25], which facilitate the rejection of proliferation and differentiation of malignant cells. For example, the C16Y peptide can bind to the integrin α5β1 receptor, which is highly expressed in tumor tissues. Dinget al. [26] coupled 3-diethylamino-propyl isothiocyanate (DEAP) to the antitumor peptide C16Y (Table 1). Interestingly, the prepared DEAP-C16Y peptide could self-assemble into spherical nanocarriers, which inhibited tumor cell growth and invasion by inactivating adherent spot kinase, blocking the PI3K-Akt pathway and invasive pseudopod formation. The DEAP-C16Y peptide was released in an acidic tumor environment to bind to α5β1, and loaded with hydrophobic DOX to target mammary tumor vessels in 4T1 mice, thereby inhibiting tumor angiogenesis and endothelial cell metastasis.

2.1.1. Integrin receptors

Integrins are families of membrane surface receptors consisting of multiple heterodimeric cell surface receptors that promote tumor cell metastasis and tumor vascularization, and regulate tumor cell growth and differentiation [27]. CTPs can target integrin-overexpressing tumor tissue and inhibit angiogenesis [28]. The tripeptide sequence arginine-glycine-aspartic (RGD) is a component of cell membrane fibronectin that functions as a tumor-targeting peptide to deliver antitumor drugs. It can activate the integrin receptors αvβ3, αvβ5, αvβ6, and α5β1 on endothelial cells and tumor cells [29], with specific affinity for αvβ3 and αvβ5, and controls the release of drugs to kill cancer cells. Since integrins can act as targets against tumor angiogenesis, developing integrin ligands containing RGD motifs can be harnessed to target positive tumor cells [30]. In this respect, it has been shown that the tumor-penetrating cyclic peptides iRGD (CCRGDKGPDC) generated by the binding of RGD and CendR motifs has high affinity for αvβ3 and αvβ5 receptors. iRGD-DOX coupling modifies liposomes to enable penetration up to 90 μm of 4T1 tumor spheroids, equivalent to 12 cell layers, enhancing the active effect against 4T1 breast cancer cells [31]. The covalent binding of the alanine-alanine-aspartate "tail" residue to iRGD (CCRGDKGPDC) results in the formation of nRGD. Loading nRGD into liposomes containing DOX exhibited potent antitumor activity in mice with 4T1 breast cancer. Remarkably, 44.4% of the mice survived without disease for over 90 days throughout the experiment [32]. This indicates the ability of nRGD-loaded DOX liposomes to effectively inhibit tumor cell proliferation and angiogenesis.

2.1.2. CD13 receptor

CD13 is a highly expressed receptor in tumor cells with catalytic activity that promotes angiogenesis and metastasis in breast cancer cells [33]. Asparagine-glycine-arginine (Asn-Gly-Arg, NGR), a tumor-targeting peptide, exhibited a highly specific binding ability to tumor tissues highly expressing CD13 by phage library screening technology [34], inhibiting tumor angiogenesis and inducing apoptosis in tumor cells, improving the cure rate of cancer. Liu et al. [35] constructed matrix metalloproteinase (MMP)-triggered αvβ3 and APN dual-targeted coassembled micelle-liposome NPs (RPM@NLQ) by coencapsulating anti-fibrotic quercetin (Que) and PTX-carrying RGD micelles (RPM) into liposomes and modifying them with NGR peptides as the targeting fraction. This study was performed by intravenous injection of RPM@NLQ into the 4T1/CAF tumor-bearing BALB/c mouse model. Results showed that the average particle sizes of RPM and RPM @ NLQ were 18.2 nm and 103.1 nm, respectively, which facilitated penetration of tumor cells. RPM@NLQ achieved tumor site accumulation and drug release under NGR-directed and MMP cleavage. The cumulative release of Que in the interstitium reached 91.87%, reducing fibrosis, and PTX release reached 83.36%, inhibiting the vascular activity of breast cancer cells, thus enhancing the therapeutic effect on breast tumors. iNGR is a peptide that combines the NGR motif with the CendR motif, resulting in a novel peptide sequence that specifically recognizes the endothelial vasculature of CD13-overexpressing glioblastoma

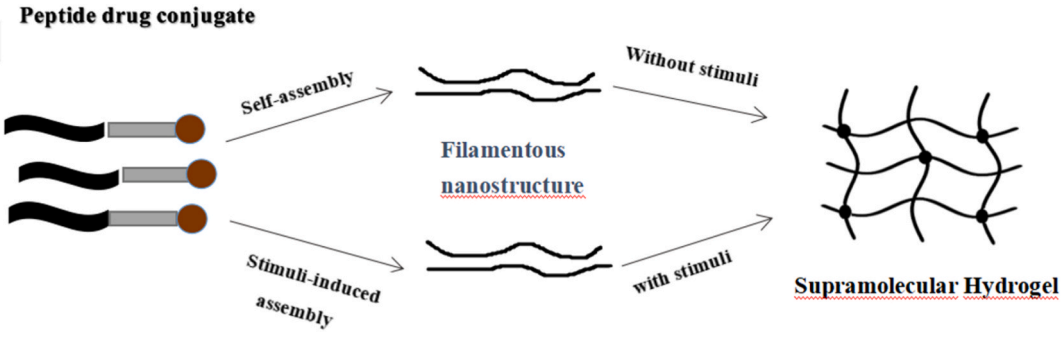

Fig. 2. Schematic diagram of hydrogel formation based on PDCs. PDCs undergo molecular self-assembly and form supramolecular hydrogels through a spontaneous or stimulus-directed assembly process.

Table 1
CPT-based DDSs for cancer treatment.

Cell-targeted peptides	Cargo	Targeted location	Ref
RGD	DOX	Tumor vascular cells	[20]
THP F3	PTX	Glioblastoma cells	[21,22]
	DDP-PAA	ID8-VEGF	
DEAP-C16Y	DOX	Mouse breast cancer cells 4T1	[26]
RGD NGR	PTX	Mouse breast cancer cells 4T1	[35]
	Que	Cancer-associated fibroblasts (CAFs)	
iNGR	DTX	Glioblastoma cells U87MG	[37]
Angiopep-2 (ANG)	BDMC	Toll-like receptors (TLRs)	[42]
		NOD-like receptors (NLRs)	
WMW10	PTX	Mouse breast cancer cells 4T1	[43]
BP9a	DOX	Human hepatocellular carcinomas HepG2	[45]
M-E5	DOX	Human acute myeloid leukemia (AML) cell line	[48]
	DTX		
IELLQAR	SN38	Human colon cancer cells HCT116	[49]
Ir@SiO_2-Gd-RGD	Iridium	Mouse colon cancer cells CT-26	[54]
	Gadolinium	Human cervical cancer cells HeLa	
RADA16	PTX	Breast Cancer Cell LinesMDA-MB-435S	[58]
Fmoc-RGD	MNP	Subcutaneous tissue of mice	[61]
TH-RGD (TR)	HCQ	Mouse embryonic fibroblasts NIH 3T3/ Human pancreatic cancer cells BxPC-3	[64]
	PTX		
cRGDfK	GEM	SKOV-3 Human Ovarian Cancer cell line	[65]
AXT050	PLGA-PEG	Triple-negative breast cancer cells MB-MDA-231	[66]
iNGR-LPNs	DOX	Mouse breast cancer cells 4T1	[67]
GNPs	exenatide	Pancreatic α-and β-cells	[68]
M2pep	NVP-BEZ 235	Murine pancreatic cancer cell line PAN 02 and M2-TAMs	[70]
	siRNA		
P	Gd^{3+}-P1	*Staphylococcus aureus*	[71]
PEG-QK	GCD	VEGF receptor	[72]
Ac-TC14012	[^{18}F]NFP	C-X-C family hyperchemokine receptor 4 (CXCR4)	[78]
	[^{18}F]SFB		
YIGSR	RhB	Melanoma cell B16F10	[81]
Phycocyanin	Lutein	Intestinal Peyer's patches	[85]
RS	Oxaliplatin	Non-small cell lung	[86]
		Hepatocellular carcinoma	
Boc-Trp-Leu-Trp-Leu-OMe	Curcumin	Cancer cells	[87]
PS1 PS2	DOX	A549 lung cancer cell	[88]
CD47	Amphotericin B	Cryptococcal meningitis	[89]
PA1	DOX	The breast cancer epithelial cell line MCF7	[90]
GE11	siRNA	Human colon cancer cells LS174T	[91]
Apoe	Flurbiprofen (FP)	C6 glial cells	[92]
		Human umbilical vein endothelial cells HUVECs	
		Immortalized brain endothelial cells (bEnd.3)	
BP9	PTX	Human hepatocellular carcinomas HepG2	[93]
RNAi-M2pep-AuNP	siRNA	Human lung adenocarcinoma cells A549 and TAMs	[94]
PBLG	DOX	Mouse breast cancer cells 4T1	[95]

cells. iNGR has higher tumor penetration and targeting properties mediated by the CendR motif targeting neuropilin-1 (NRP-1) receptor [36]. Zhou et al. [37] prepared iNGR-modified DOX liposome nanocarriers (iNGR-SSL/DOX) with a particle size of 100 nm, which facilitated targeting tumor sites. In vivo experiments in tumor-bearing mice showed that iNGR-SSL/DOX could be effectively taken up by glioblastoma U87MG cells and targeted to the CD13 receptor, which increased the accumulation of the anticancer drug DOX and the targeting of tumor therapy.

2.1.3. Epidermal growth factor receptor

EGFR is a transmembrane protein receptor that is over-expressed on various malignant cellulae and can be used as an uptake system for targeted delivery [38]. Current evidence suggests that the GE11 peptide can target cancer cells with high expression of EGFR. Song et al. [39] demonstrated that GE11-DOX liposomes could specifically targets EGFR-overexpressing human non-small lymphocyte lung cancer cells H1299 and human lung adenocarcinoma lymphocyte SPCA1 by cell experiments. Compared with free DOX and non-targeted DOX liposomes, GE11-DOX exhibited higher cytotoxicity against cancer cells. Moreover, fluorescently labeled GE11-DOX showed a significant accumulation signal at the tumor site in H1299 mice. Thus, it was concluded that GE11 could enhance the targeted therapeutic ability of DOX. Chen et al. [40]prepared multifunctional redox-sensitive nanogels (EGFR/CD44-NGs) with a small size of 165 nm using nanoprecipitation and photoclick chemistry. The nanogels consisted of tetrazole, GE11, and methacrylic acid semiamide and carried particle enzyme B (GrB) drugs with intracellular targets. At low doses of 3.85 nmol GrB equiv/kg,

EGFR/CD44-NGs-GrB almost completely inhibited the growth of the human ovarian cancer cells SKOV-3 without producing any toxic side effects.

2.1.4. Extracellular matrix

Therapeutic agents can be delivered to diseased tissues via peptides targeting extracellular matrix (ECM) receptors [41]. Cuesta et al. [42]developed a star-crosslinked polyglutamic acid (StCl)-propargylamine (Pr)-bisdeoxymethoxycurcumin (BDMC) nano-coupling (StClPr-BDMC-ANG) based on the targeting peptide Angiopep-2 (ANG) targeting Toll-like receptors (TLRs) and NOD-like receptors (NLRs). StClPr-BDMC-ANG could penetrate the blood-brain barrier (BBB). It was demonstrated by in vivo experiments that StClPr-BDMC-ANG was able to protect the activity of progenitor glial cells in the chronic ethanol depletion model in mice, and attenuate the inflammatory pathway mediated by signaling pathways, such as TLR4/NF-κB, through inhibiting ethanol-induced up-regulation of key inflammatory mediators and down-regulation of microRNAs. This not only alleviated the alcohol-induced neuroinflammation, but also gave full play to the targeted therapeutic effect of curcumin. Yu et al. [43]prepared an assembled synergistic peptide-drug couplers (asPDCs), which were co-assembled from the selective peptide WMWVTNLRTD (WMW10) and PTX-WMW10 coupler to form asPDCs WMW10, which was able to target DLC1 protein and hydrolyze PIP2 protein by releasing the protein PLCδ1, which facilitated actin filament depolymerization and suppressed cell migration, and PTX, which could stabilize microtubules by anchoring the inner surfaces of microtubules. In vitro experiments showed that asPDCs WMW10 had significant toxic effects on 4T1 breast tumor cells. In vivo experiments demonstrated that the asPDCs WMW10 and WMW10 showed stronger fluorescent signals at the tumor site of 4T1 breast cancer-loaded mice compared with PTX-WMW10, indicating that asPDCs are tumor-targeted and asPDCs can accurately deliver the anticancer drug PTX to the tumor site and inhibit tumor cell proliferation. In addition, asPDC could inhibit tumor cell metastasis and invasion through microfilament depolymerization and microtubule stabilization, reflecting the combined therapeutic effect of asPDC on tumor cells.

2.1.5. Other receptors

It has been established that tumor cells exhibit a high level of expression of the transferrin receptor (TfR) on their surface. Urbiola et al. [44] used the specific targeting peptide B6 of TfR to form a nano-coupled peptide with 2 kDa PEG and polyamidoamine (PAMAM). This nonviral vector can transport therapeutic siRNA to LS174T human colon cancer cells, increase gene silencing ability, and reduce the average expression of luciferase by 20%. Thus, they can inhibit cancer cell proliferation and metastasis and demonstrate excellent gene delivery ability, providing a new direction for treating cancer caused by gene mutations. Liu et al. [45]developed DOX-ami-PEG 5000-SS-BP9a by linking DOX through a PEG-containing bridging structure to the TfR-targeting peptide analog BP9a (CAHLHNRS). The half-life of DOX-ami-PEG 5000-SS-BP9a in human serum was 1.92 ± 0.13 h, while the half-life of YSA-L1-PTX coupling, which is also composed of the L-configuration Amino acid EphA2 receptor targeting peptide YSA (YSAYPDSVPMMS) and PTX through the triazole ester type small molecule linker arm, was only 23 minutes in rat plasma [46],suggesting that DOX-ami-PEG 5000 –SS–BP9a enhanced drug biological stability. Moreover, the toxicity of BP9a–SS–DOX to TfR low-expressing human normal hepatocytes L-02 was lower than that of DOX, while the cytotoxicity to human hepatoma cells HepG2 was greater than that of DOX, indicating that BP9a could improve the selective killing ability of DOX on HepG2 cells [47].

The C-X-C chemokine receptor 4 (CXCR4) is expressed in acute myeloid leukemia (AML) cells. Zhang et al. [48] prepared M-E5-DOX nanomicelles by mixing DSPE-mPEG2000 aqueous solution, CXCR4 antagonistic peptide E5, and DOX aqueous solution using vortex ultrasonication. It was found that M-E5-DOX could specifically bind to AML U937 and DOX-resistant HL60/A cells, significantly downregulating the CXCR4-mediated signaling pathway in vitro cellular experiments. During 0–4 h, the plasma concentration of DOX increased from 0.9 μM to 3.52 μM, showing an increasing trend and enhancing the internalization of DOX. Importantly, M-E5-DOX could reduce the number of leukemia lymphocytes in the medulla ossea of AML mice using the targeting and DOX toxic effects of the antagonist peptide, providing hope for more effective approaches against refractory AML.

It has been established that E-selectin is a highly expressed receptor in tumor vascular endothelial cells. To inhibit tumor angiogenesis, Fu et al. [49]combined PEGylated E-selectin binding peptide (IELLQAR) with the parent drug SN38 of irinotecan to synthesize amphiphilic PDCs as a nanoprodrug, which further self-assembled into NPs in an aqueous environment. IELLQAR could actively target the E-selectin receptor and enhance the permeability and retention (EPR) effect, which allowed NPs to accumulate and remain at the tumor target site, restraining the diffusion and metastasis of human colon cancer cells (HCT116) and extend the survival of primary HCT116 mice. Besides, the TH19P01 peptide (Ac-GVRAKAGVRN-Nle-FKSESY)-docetaxel coupling (TH1902) exhibited high affinity with the sortilin 1 (SORT1) receptor overexpressed by triple-negative breast cancer (TNBC) and was shown in ex vivo experiments to target SORT1 and release the anticancer drug docetaxel. Cellular experiments demonstrated that TH1902 could target SORT1 and release the anticancer drug docetaxel, which promoted apoptosis of TNBC-derived MDA-MB-231 lymphocyte in vitro, TNBC-derived HCC-70 lymphocyte and 4T1 breast cancer lymphocyte in a mouse xenograft model in vivo [50], with high in vivo efficacy against TNBC, and could be used for the safe treatment of TNBC. In contrast, another luteinizing hormone-releasing hormone (LH-RH) receptor is reportedly overexpressed in breast, ovarian, melanoma, and prostate cancers. It was found that DOX or 2-pyrroline-DOX coupled to the LH-RH receptor-targeting peptide AN-207 could enhance the targeting of DOX to cancer cells [51].

2.2. Application of the CTP-based drug delivery system

DDSs incorporating targeted peptides overcome obstacles to drug transportation in diseased tissues, allowing for precise and effective drug delivery to the intended target tissues [52]. Nano-drug delivery systems (NDDs) are assembled into nanoparticles by various excipients, which in turn encapsulate the therapeutic drug and passively or actively deliver the drug to the target cells. NDDs

not only exert anticancer effects by enhancing the permeability retention effect of the drug in tumors, but also reduce toxicity by decreasing the accumulation of the drug in normal organs through the long body circulation [24].The utilization of nanocarriers consisting of cell-targeted peptides facilitates the binding of both hydrophobic and hydrophilic bioactive molecules [53], enabling the specific targeting of therapeutic agents to desired sites. Cheng et al. [54] prepared a multifunctional nanoprobe Ir @SiO_2-Gd-RGD NPs targeting photoluminescence (PL) and magnetic resonance dual-modal imaging by coupling iridium (III) complex, gadolinium (III) and RGD onto silica nanoparticles (SiNPs). Compared with Ir @ SiO_2-Gd NPs, Ir @ SiO_2-Gd-RGD NPs have better biocompatibility and PL/MR dual-modality imaging ability for HeLa cells and CT-26 tumor-bearing mice, indicating that Ir @ SiO_2-Gd-RGD NPs have important value in the field of future cancer diagnosis and treatment.

Functional peptides include four kinds of peptides: targeting peptides, microenvironment-responsive peptides, cell-penetrating peptides, and therapeutic peptides, which are characterized by short half-life, poor stability, and easy to be hydrolyzed by proteolytic enzymes and cleared by the liver and kidney organs [55]. The multifunctionality of peptides is reflected in the ability of the functional unit to covalently couple with the drug under the action of a linker to form a system of PDCs [13]. PDCs have a strong drug delivery capacity and an enhanced drug activity effect; however, as the drug is prone to induce a toxic response in normal cells after systemic administration, localized administration is required to overcome these limitations. Hydrogels have a unique three-dimensional cross-linked network structure and injectability that facilitates local drug delivery strategies for lesions [56], while PDCs can assemble into supramolecular hydrogel systems under acidic stimulation (Fig. 2). Functionalized modification of hydrogels by functional peptides resulted in better biocompatibility and drug delivery efficiency [57]. Peptides can form hydrogels and be functionally modified through non-covalent interactions such as hydrogen bonding, electrostatic interactions, hydrophobicity, and π-π conjugation, and the preparation of hydrogels into supramolecular nanomicrospheres can enhance the loading capacity of drugs and achieve controlled drug release. Liu et al. [58]investigated a self-assembled peptide RADA16 solution, which was loaded with PTX and had a controlled release effect on it, and the conjugate of the two was able to self-assemble into a supramolecular hydrogel, which was conducive to the delivery of anticancer drugs and inhibited the proliferation of a breast cancer cell line, MDA-MB-435S, effectively. Parkins et al. [59]developed a peptide-functionalized hyaluronic acid (HA) hydrogel DDS for the treatment of xenograft glioblastomas by first functionalizing the peptide residues cysteine-phenylalanine based on the HA polymer backbone, and then forming a hydrogel after physical cross-linking with cucurbituril (CB) to improve the efficiency of drug utilization. Gallo et al. [60]prepared N-fluoromethoxycarbonyl diphenylalanine (Fmoc–FF)–(FY)3 and Fmoc–FF–PEG8-(FY)3-coupled polypeptide hydrogel (HGs) systems according to the "solvent-switch" method, wherein (FY)3 serves as a hexapeptide framework with alternation of three tyrosine (Y) and three phenylalanine (F) residues. In addition, a coupled peptide nanohydrogel (NGs) system was prepared by submicronization of HGs according to a top-down methodology. The coupled peptide HGs and NGs were able to better load the anticancer drug DOX, and the coupled peptide NGs showed a 20% increase in the release rate of DOX compared to pure NGs. DOX-loaded HGs and NGs resulted in a survival rate of only 49–57% for the MDA-MB-231 breast cancer cell line, which was significantly lower than that of cells with empty HGs and NGs, indicating that the peptide-based HGs and NGs system can deliver toxic drugs to tumor cells or tissues, and that this novel peptide-based supramolecular hydrogel system is expected to replace the traditional liposomal supramolecular system to precisely achieve the targeted drug delivery for clinical diseases. Mari et al. [61]prepared magnetic hydrogels by incorporating magnetic nanoparticles (MNP) into hydrogels prepared from fluorenylmethoxycarbonyl (Fmoc)- diphenylalanine (Fmoc- FF) and Fmoc-RGD short peptides. In ex vivo experiments, the magnetic short peptide hydrogels showed good biocompatibility and non-toxicity. In addition, after magnetic hydrogels were injected subcutaneously by mice, anisotropy could be induced by an external magnetic field to modulate the physical properties and three-dimensional structure of the short peptide hydrogels, among others. In conclusion, MNP enhanced the structural stability and injectability of short peptide hydrogels, provided excellent peptide carriers for minimally invasive injectable surgery, and expanded the application prospects of short peptide hydrogels in biomedical fields.

Liposomes (Lips) are nanoparticles composed of phospholipid bilayers that protect the chemical structure of peptide molecules from damage [62]. Interestingly, it has been reported that liposome-modified NGR and RGD peptides could enhance the recognition of tumor cell targets [63], improving the targeting effect of the drugs. Arap et al. [20]first used nanoliposome-modified RGD-DOX couples to target tumor-vascular cells to treat rhabdomyosarcoma mice. Chen et al. [64] developed a multifunctional peptide by combining a pH-sensitive TH peptide and a cRGD peptide in tandem, forming TH-RGD (TR), which was capable of targeting pancreatic cancer cells with high expression of αvβ3 receptors. They also developed a drug delivery platform called TR-Lip, which was modified with liposomes and able to encapsulate both the autophagy-inhibiting drug hydroxychloroquine (HCQ) and an anticancer drug for targeted delivery. In a mouse model, human pancreatic cancer cells BxPC-3 showed 11.54-fold greater uptake of TR-Lip than PEG-Lip, further inhibiting autophagy in pancreatic cancer cells and surrounding tumor-associated fibroblasts (CAFs) in an acidic tumor environment. TR-Lip penetrated approximately 120 nm into the tumor sphere, enhancing the treatment of dense mesenchymal pancreatic cancer. Kulhari et al. [65]prepared polymer DDSs on the surface of liposomes consisting of the targeted cyclic pentapeptide cRGDfK conjugated with the anticancer drug gemcitabine (GEM), which could carry αvβ3 specifically targeted to SKOV-3 human ovarian cancer cellulae. Even at low doses of 0.01 μg/mL, the intracellular drug concentration was high, resulting in only 56.9% cancer cell survival. This finding substantiates that DDS enhances the antiproliferative ability of the drug.

PEG is a simple water-soluble polymer that can modify peptide-drug conjugates and enhance the inhibitory effect of drugs on target cells. It is well-established that AXT050 is a tumor cell-targeted peptide that targets the αvβ3 integrin receptor, exerting antitumor and antiangiogenic effects. Bressler et al. [66]conjugated this peptide to the surface of poly(lactide-*co*-glycolide)-*block*-polyethylene glycol (PLGA-PEG) NPs. The tumor-targeting effect and the density of the surface-bound AXT050 peptide were correlated. The PLGA-PEG-AXT050 NPs with 10% peptides surface coating extended the half-life by 103 min in triple-negative breast cancer cells (MB-MDA-231) and accumulated 14% of the AXT050 dosage, thereby killing cancer and endothelial cells. To improve the absorption rate of medicines by malignant cells and control the release of drugs in cells, Ye et al. [67]prepared intelligent nanoparticles composed

of a PEGylated lipid monolayer shells and a pH-sensitive hydrophobic poly-L-histidine (pHis) nucleus. The nanoparticles filled with DOX were conjugated with iNGR to form iNGR-LPNs, which expanded in the tumor microenvironment (pHe: 7.0 – 6.5) and increased DOX uptake by 4T1 mouse breast cancer cells. Under acidic endolysosomal conditions (pHendo: 6.5 – 4.5), the NPs dissociated and caused endolysosomal escapes, allowing for controlled DOX release into the cytoplasm. Han et al. [68]assembled two carriers, low molecular weight protamine-deoxycholic acid (LMWP-DCA) and poly(sialic acid)-PEG-glycocholic acid (PSA-PEG-GCA), to prepare a novel dual-bile acid functionalized small-sized nanoparticle (GNP) with a dimension of 140 nm, to allow the targeted conveyance of the GLP-1 analog exenatide to pancreatic α cells and β cells in type 2 diabetes mellitus, prolonging the efficacy of plasma glucose reduction in vivo.

It is now understood that tumor-associated macrophages (TAMs) generally exhibit the pro-tumor M2 phenotype in the tumor microenvironment (TME), accelerating malignant cells proliferation and dissemination by stimulating tumor inflammation and disrupting antitumor immunity, often leading to adverse outcomes [69]. Li et al. [70] developed self-assembled nanomicrospheres modified with the targeting peptide M2pep to obtain a DDS capable of simultaneously encapsulating and delivering TAM colony-stimulating factor-1 receptor (CSF-1R)-siRNA and the PI3K-γ suppressant NVP-BEZ 235 for targeting M2-type TAMs. This dual drug-loading nanosystem could activate antitumor immune responses by blocking PI3K-γ and downregulating CSF-1R, which helped to "purify" the tumor immune microenvironment, thereby inhibiting the growth of the murine pancreatic carcinoma cell line PAN 02 and enhancing the anti-pancreatic cancer effect.

Magnetic resonance imaging (MRI) is used as a non-invasive clinical imaging technique for the diagnosis and treatment of diseases. Li et al. [71]developed an in situ highly sensitive MRI technique subjected to matrix metallopeptidase 2 (MMP-2) stimulation in the bacterial microenvironment in vivo in response to and imaging of bacterial infections based on a peptide-modified magnetic resonance modulation (MRET) probe (MPD-1), a magnetic nanoparticle (MNP) composed of a gadolinium ion (Gd^{3+})-modified MMP-2-cleavable self-assembling peptide (P1) and a bacterial-targeting peptide (P) consisting of a MNP. When MPD-1 was targeted to the bacterial infectome, P1 was cleaved by MMP-2, and the MPD-1 assembly was disassembled into MNP monomers, which were further separated from Gd^{3+}. The MNP monomer structure and the separation of Gd^{3+} from MNP (MRET OFF) phenomenon resulted in a further restoration and significant enhancement of the T1 MRI signal. The peptide-based MPD-1 probe achieved high sensitivity (104 CFU) MRI for *S. aureus* at the site of myositis, as well as the ability to accurately diagnose sterile inflammation and bacterial infection. This demonstrates the potential of this probe for early bacterial infection diagnosis in the clinical setting. Li et al. [72]prepared PEG-vascular endothelial growth factor (VEGF)-mimetic peptide QK-modified gadolinium-doped carbon dot nanoprobes (GCD-PEG-QK), in which the VEGF receptor was overexpressed in myocardial infarcted hearts and specifically bound to the VEGF-mimetic peptide QK. In a mouse model of myocardial ischemia/reperfusion (I/R), mouse models injected with GCD-PEG-QK showed significant signal enhancement in the infarcted region of the myocardium and displayed accurate MRI of myocardial infarction. In addition, in vivo studies demonstrated that GCD-PEG-QK further enhanced the repair of angiogenesis by QK peptides by targeting the infarcted myocardium and delivering QK and enhanced the effect of QK peptides on the I/R-induced myocardial injury. This study pioneered the use of QK peptide-coupled nanoprobes as cardiac MRI contrast agents for the diagnosis of myocardial infarction and created a noninvasive and highly effective MRI and therapeutic approach for acute myocardial infarction.

Chemical exchange saturation transfer imaging (CEST), a contrast mechanism for MRI, provides a wealth of molecular-level information with MRI sensitivity [73]. CEST is able to detect the magnetization of large amounts of water when the exchangeable spins of endogenous or exogenous molecules are selectively saturated by appropriate RF pulses, and this saturation is transferred to the bulk spins in the presence of chemical exchanges, resulting in a reduced MRI detectable water signal and the ability to indirectly image low concentrations of chemicals. Gregorio et al. [74]prepared cationic hexapeptide Ac-K1 and Ac-K2 hydrogels loaded with iopamidol contrast agent, which were not only non-toxic to the tumor cell lines GL261, TS/A, and 3T3-NIH and to Balb/c mice inoculated with mammary tumor cells TS/A were non-toxic effects and injectable, but also in vitro CEST-MRI experiments demonstrated that the CEST contrast rate of iopamidol was higher than 50%, which indicates that this peptide-based hydrogel has the ability to retain imaging probes in vitro. Ac-K1 and Ac-K2 hydrogels containing iopamidol as efficient CEST-MRI probes demonstrate, for the first time, the use of peptide-based hydrogel systems in novel biomedical imaging procedures based on CEST-MRI detection. CEST-MRI imaging has been frequently investigated for its characterization in oncology as a valuable expansion of molecular imaging and quantitative biomarker libraries. Amide proton transfer weighted (APTw) MRI, a subgroup of CEST, utilizes the saturable exchange of amide chemical groups, mainly at 3.5 ppm [75]. Meng et al. [76]compared the effect of diffusion kurtosis imaging (DKI) and amide proton transfer-weighted (APTw) imaging in the differential diagnosis of benign breast lesions and breast cancer in 133 patients with breast lesions, The mean standardized magnetization transfer ratio asymmetry (MTRasym) value used to measure the effect of CEST was higher in benign breast lesions, indicating that the predictive diagnostic imaging of CEST-MRI in benign lesions was more pronounced than that in cancerous lesions. In addition, higher MTRasym and more significant molecular imaging were observed in high-grade cancers compared to low-grade cancers.

Peptide-based targeted positron emission computed tomography (PET) probes have high affinity and specificity for specific target cells and can be modified into different PET probes. Radionuclides are radioisotopes of elements that are used in medical imaging and cancer therapy [77]. Radionuclides (e.g., 18F, 11C) can covalently bind to the peptide to form a radiolabeled peptide-based probe, or another ligand that is strongly complexed to a radioisotope (e.g., 64Cu, 68Ga) via multiple ligand bonds can be chemically conjugated to the peptide delivery portion. Zhang et al. [78]synthesized the 18F-labeled Ac-TC14012 radiocoupler probes 4-nitrophenyl 2-[18F]-fluoropropionic acid ([18F]NFP)-Ac-TC14012 and N-succinimidyl-4-[18F]-fluorobenzoate ([18F]SFB)-Ac-TC14012 in DMSO, wherein Ac-TC14012 is a peptide with high affinity for the C-X-C family of superconditioning factor receptor 4 (CXCR4) that is highly expressed in tumor cells. The radiochemical yields (RCY) of the two probes were 38.1 ± 10.5% and 31.6 ± 7.0%, respectively, and their radiochemical purities (rcp) were ≥95%. The specific activity of the [18F]NFP-labeled peptide was 13.6–17.6 GBq μmol^{-1} (at

the time of measurement), whereas the other was 18.7–31.6 GBq μmol^{-1}. Compared to the [18F]SFB-labeled peptide, the [18F]NFP-labeled peptide had higher tumor uptake and better specific binding, and had significant imaging effects on tumor cells. Liu et al. [79]coupled a carboxylic acid group-containing BaBaSar chelator with an RGD peptide to form a BaBaSar-RGD coupling, and BaBaSar-RGD2 was isolated and purified in 78% yield by high-performance liquid chromatography (HPLC), which further showed that the radiochemical yield and specific activity of 64Cu-labeled BaBa-Sar-RGD2 were 90.7 ± 5.1% (n = 4) and 200–500 μCi μmol^{-1} (5.4–13.5 GBq μmol^{-1}), and 64Cu-BaBaSar-RGD2 exhibited high stability and tumor uptake in vitro and in vivo. In addition, 64Cu-Ba-BaSar-RGD2 had a promising application as an integrin marker with good biodistribution and safety in PET-carrying monkeys.

Fluorescence imaging (FI) technology is widely used for cancer detection and diagnosis and treatment, and is a low-cost, highly specific and sensitive early cancer diagnostic technique that can be used to replace MRI, positron emission computed tomography (PET), and other imaging techniques that require costly equipment and are radioactive in nature [80]. Liu et al. [81]synthesized the pentapeptide tyrosine-isoleucine-glycine-serine-arginine (YIGSR)-rhodamine B derivative (YIGSR-RhB) and the tripeptide arginine-glycine-aspartic acid (RGD)-rhodamine B derivative (RGD-RhB) by solid-phase synthesis, respectively, which were two novel peptides fluorescent imaging probes that could accurately target laminin and fibronectin receptors that were overexpressed in the ECM of tumor tissues. As demonstrated by in vivo experiments, YIGSR-RhB and RGD-RhB were highly absorbed by melanoma cells B16F10 and 4T1 breast cancer cells and had obvious red fluorescence imaging in these tumor cells in vitro and in mouse models in vivo, which indicated that YIGSR-RhB and RGD-RhB could be used as a tumor-targeted imaging probe and improved tumor targeting, which was expected to be a powerful tool for specific targeting of tumor cells and for the diagnosis and detection of cancers in the clinic. Self-assembled peptide nanoprobes are stimulus-responsive to the microacidic environment of tumor tissues and are highly sensitive imaging probes that target the tumor microenvironment. Nanoprobes self-assembled from oligopeptides can dissociate with small changes in pH of the tumor microenvironment, and then be activated into nanostructures with fluorescent properties for tumor cell-specific diagnosis and intra-tumor imaging, and are an excellent pH-responsive drug delivery system for drug enrichment and release at the target site. Zhao et al. [82] investigated a novel biomimetic nanoprobe based on peptide self-assembly, which responsed and was activated when small changes occur in the low-acid environment of tumor tissues for imaging and diagnosis of the interior of tumors, carrying therapeutic drugs for accurate delivery to the tumor tissues. Aiming at the heterogeneity and high mutation rate of tumor cells, Ji et al. [83]created self-assembled peptide-antibody immunocouplings, which covalently coupled antibody drugs with pH insertion peptide (pHLIP), and took advantage of the structural changes of pHLIP peptide in the tumor microacidic environment to deliver antibody drugs to the surface of the tumor cells, activating the killer cell-dependent-mediated toxicity effect of the antibody drugs, which in turn killed a wide range of breast cancer cells, and could inhibit the growth and metastasis of the tumor cells at an early stage.

The interaction forces that induce self-assembly of peptide molecules mainly include electrostatic interactions, hydrogen bonding, ionic bonding, π-π stacking, and other non-covalent interactions, which are essential for the formation of stable self-assembled structures of molecules [84]. Liu et al. [85]prepared oral lutein NPs specifically binding to the dectin-1 receptor by layer-by-layer self-assembly of cationic chitosan, phycocyanin, and 3-carboxyborobenzoic acid-modified yeast β-glucan via electrostatic interactions. The NPs specifically targeting intestinal Peyer's patches attenuated corneal damage in dry eye disease (DED) model mice, and increased the bioavailability of lutein in plasma and eyes of Balb/c mice by 2.63-fold and 1.81-fold, respectively. In conclusion, self-assembled lutein nanoparticles improved the oral delivery strategy of lutein during DED intervention. NGR specifically targeted the CD13 receptor of tumor endothelial cells, but did not possess the ability to target the nucleolus of tumor cells. Jing et al. [86] demonstrated that the RS peptide, which evolved from the hepatocellular carcinoma (HCC)-targeting peptide P47, had a molecular imaging role, and that the RS probe provided up to 21-fold contrast for imaging HCC micrometastases in non cancerous tissues from in situ model mice and patient biopsies. In addition, RS targets a series of cancer cells, such as non-small cell lung (NSCLC) and HCC, and localizes to the nucleolus kernel position of the cell nucleus; therefore, RS-Oxaliplatin (RS-OXA) coupling can induce nucleolus kernel stress response and fully exerts the tumor-blocking effect in HCC mice, and fluorescently-labeled RS can also dynamically observation of subcutaneous tumor growth in HCC mice under RS-OXA treatment. Taken together, this demonstrated that RS targeted a broad spectrum of tumors with high specificity and sensitivity. Thus, RS was able to target deliver OXA to the tumor site in HCC mice, providing a versatile means for tumor imaging and targeted therapy. Pandit et al. [87]reported that the concentration-dependent tetrapeptide Boc-Trp-Leu-Trp-Leu-OMe self-assembles to form discrete nanospheres at low concentrations, which gradually fused and aggregated to form microspheres with increasing peptide concentration. The peptide nanomicrospheres encapsulate the hydrophobic dye carboxyfluorescein and the anticancer drug curcumin through aromatic interactions between the side chains of tryptophan residues on the outer surface, and the drug is released when the peptide self-assembled structure is disrupted by stimulation with potassium ions and acidic conditions. Such short peptide self-assembled structures with dual drug encapsulation and delivery capabilities are a promising class of drug delivery carriers. Peptide-based self-assembled nanostructures are generally composed of natural amino acids and have good biocompatibility. Sivagnanam et al. [88]prepared tyrosine-tryptophan (Tyr-Trp) dipeptide-based nanoparticles (DPNPs) composed of Boc, whose structure was hardened by Zn(II) and altered the intrinsic optical properties of peptide-based nanoparticles, which made dipeptide-based fluorescent nanostructures have the potential to be developed as new imaging probes. In addition, the Boc-Tyr-Trp dipeptide-based DPNPs PS1 (Boc-Tyr-Trp-OMe) and PS2 (Boc-Tyr-Trp-OH) could load chemotherapeutic drug DOX and facilitate intracellular drug delivery. PS1 and PS2 were chemically modified with the EPCAM aptamer, which enhanced specific delivery of DOX to A549 lung cancer cells and did not deliver to cardiomyocytes, thus ensuring the safety of the drug for clinical use. This suggests that short peptide-based fluorescent nanostructures hold great promise for the exploitation of novel targeted drug delivery vehicles. These photostable DPNPs are expected to enable real-time monitoring of drug release and cellular uptake in the future. Tang et al. [89]designed a system to overcome reticuloendothelial system (RES) blockage through a "don't-eat-us" strategy. First, upon intravenous administration of a D-self-peptide-labeled liposome (DSL)-modified mouse

CD47 protein-derived enzyme-resistant peptide ligand, the DSL wrapped around liver phagocyte membranes and reduced interactions. DSL significantly prolonged the half-life of the injected nanoparticle carrier compared to blank liposomes. In brain-targeted administration of cryptococcal meningitis model mice, this strategy demonstrated that DSL promotes brain-targeted therapeutic efficacy and brain accumulation of the drug amphotericin B. This suggests that the strategy of blocking RES by masking the phagocytic surface had the utility of enhancing nanoparticle delivery. Sivagnanam et al. [90]successfully synthesized a cationic tripeptide, Boc-Arg-Trp-Phe-OMe (PA1), which self-assembles into nanosphere structures in aqueous solution and undergoes a visible fluorescent property transition. In addition, these tripeptide spherical structures (TPSS) can not only trap and deliver the anticancer drug DOX into cancer cells, leading to apoptosis, but also detect the drug release in real time. Such peptide-based nanodrug delivery systems (NDDs) are proteolytically stable and biocompatible. PA1 coupled to the epithelial cell-specific epithelial cell adhesion molecule (EPCAM) aptamer (PA1-Apt) improved DOX delivery and killing in the breast cancer epithelial cell line MCF7, and similarly, PA1-Apt-DOX treatment resulted in a significant increase in DOX entry into MCF7 cells. In conclusion, peptide-based NDDs provide a superior platform for biomedical applications such as fluorescence imaging and drug delivery, and have far-reaching implications in cancer therapy.

3. Cell-penetrating peptides

The cell membrane acts as a natural physiological barrier that not only hinders the transport and delivery of molecules, such as proteins and nucleic acids, into the cell but also limits the penetration of drugs. Cell-penetrating peptides (CPPs) are small molecular peptides consisting of approximately 8–30 amino acids residues with cell membrane permeability and can cross cells without compromising the integrity of the cell membrane. Therefore, CPPSs can be used as carriers to deliver therapeutic substances such as nucleic acids, proteins, and small molecule drugs to the appropriate sites [96]. For example, TAT peptides, protein-derived CPPs containing a reverse transcription activator, can reportedly carry DOX and PTX to limit the multiplication of KB in human oral epidermoid carcinoma cells, and TAT-siRNA couples can be used for gene therapy in human chronic myeloid leukemia K562 cells [97].

3.1. Intake route

There are two main pathways for CPPs to enter cells (Fig. 3): the direct pathway relies on the polarity of positively charged CPPs to disrupt the stability of membranes and form pores, allowing CPPs to pass through the cell membrane without expending energy [98]. This includes (1) CPPs directly inserting into gaps in the cell membrane; (2) the carpet model: positively charged CPPs are flatly spread on the surface of a negatively charged film, increasing the fluidity of the membrane and the permeability of CPPs through electrostatic interactions; and (3) the inverted micelle model: the phospholipid bilayer invaginates to form micelles that encapsulate CPPs. After entering the cell, the micelles invert and release CPPs [99,100]. Li et al. [101] modified bovine lactoferrin-derived L6 (HL6; CHHHHRRWQWRHHHHHC) to directly penetrate human bronchoalveolar carcinoma A549 cells. In addition, it has been reported that cytoplasmically localized internalizing peptide 6 (CLIP6) could cross the cell membrane via a direct translocation pathway and deliver the model antigen ovalbumin (OVA) directly into the cytoplasm [102].

Endocytosis is an energy-dependent process whereby the phospholipid bilayer of the cell membrane is recessed inward and envelops CPPs in the cell. For example, Li et al. [103] demonstrated that bovine lactoferrin-derived L6 CPP (RRWQWR) could be internalized into lung cancer cells and that the L6/quantum dot (QD) complex could enter the cells via endocytosis. The ability of CPPs to penetrate depends on endocytosis and consumes energy in three main ways: macropinocytosis, caveolin-mediated endocytosis (CvME), and clathrin-mediated endocytosis (CME) [104]. The process of macropinocytosis requires cholesterol, actin and GTPases [105]. Nakase et al. [106] revealed that a single transmembrane protein called caveolin could initiate macropinocytosis. Upon

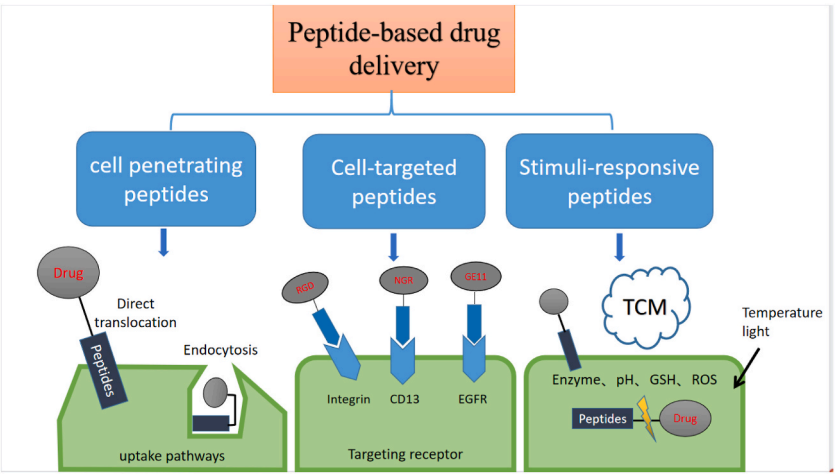

Fig. 3. Peptide-based drug delivery systems.

interaction with the cell membrane, peptides could form coaggregates that induce actin polymerization, transporting macromolecules into the cell. Neuropilin-1 (NRP1) and heparan sulfate proteoglycan (HSPG) receptors are involved in the transmembrane uptake of CPPs [107]. It has been reported that NRP1 and HSPGs could synergistically induce macropinocytosis to facilitate the transmembrane transport of CPPs. Interestingly, they interacted with different peptide NPs in the same vesicle, which promoted the conveyance of drugs to the corresponding target spot [108]. Vesicles are lipid raft invaginations of the cell membrane encapsulated in lipid chain-bound receptors such as HSPGs and scavenger receptors (SCARA) that can bind to various protein ligands such as CPPs to facilitate penetration of the cell membrane and drug delivery capacity [109]. The CME pathway involves the formation of lattice-protein-coated vesicles in the phosphatidylinositol 4,5-bisphosphate-enriched region of the plasma membrane, which is initiated by the interaction of the peptide with specific receptors on the cell surface. This pathway is involved in the intracellular delivery of CPPs, and it relies on the hydrolysis of GTP and the release of the coated vesicles [110]. It has been reported that the cell-penetrating peptide kallikrein B1 antagonist penetrating peptide (CP–B1RA) could inhibit tumor proliferation by modulating the kinin B1 (B1R) receptor, which was highly expressed in triple-negative breast carcinoma cells and thus accelerated apoptosis [111]. CPPs are internalized by endocytosis andescape from the nuclear endosome into the cytosol to avoid lysosomal degradation; for example, the pro-lysosomal drug chloroquine (CQ) enhanced endosomal escape of the searyl-(CPPs transport protein 10) TP10 and improved drug activity at the target site [99]. Nevertheless, no consensus had been reached on the mechanisms of intake and assimilation of CPPs, and in-depth research was needed to elucidate the cellular uptake mechanisms of CPPs [112].

3.2. Application of CPP-based drug delivery systems

Nanocarriers composed of CPPs are able to enhance the delivery of chemotherapeutic drugs [113]and represent an efficient DDS for drugs that cannot cross cell membranes. CPPs can enhance active barrier penetration and improve therapeutic drug killing by optimizing sequences, fusing new peptides, or forming nanostructures [114].

CPPs act as nonviral carriers for gene delivery, reducing the toxic response of the organism, and cationic CPP nanomicelle carriers can form DDSs. Their small size facilitates deep penetration into tumor cells [115], enabling gene therapy and diagnosis. For example, cationic peptide R3V6 nanomicelles composed of 3-arginine and 6-valine can be loaded with siRNA and carmustine (BCNU) to form siRNA/R3V6–BCNU complexes, which undergo size reduction to 400 nm by charge interactions [116] (Table 2) and have the ability to penetrate the cell membrane of C6 glioblastomas and deliver siRNA and carmustine in combination to therapeutic targets. It was found that CPP-modified nanocarriers could deliver nanoparticles and genes to the viable layers of the skin and hence play a significant role in transdermal drug delivery and topical drug delivery [117]. The amphipathic peptide MGPE9 (CRRLRHLRHHYRRRWHRFRC) was used to deliver plasmid DNA as a nanocomplex into the human immortalized keratinocyte cell line HaCaT [118] for the treatment of skin diseases. MGPE9 was transfected into the skin with relatively high efficiency, and the loaded plasmid DNA was continuously expressed in the skin for 48 h. Exosomes are membrane-bound nanovesicles, and peptide molecules can assist exosomes as drug delivery vehicles to overcome the low cellular uptake of drugs in gene therapy. Mangesh et al. [119]conjugated the cell-penetrating peptide YARA to a mammalian microRNA (miR-21-5p) to form a YARA-miR-21-5p conjugate and uploaded it into exocrine, which showed an 18.6-fold increase in exosome loading of YARA-miR-21-5p compared to miR-21-5p alone. Following efficient cellular uptake, the exosomes could rapidly transport the therapeutic substance miR21-5p into mammalian cells. The loading of YARA-miR-21-5p onto exosomes significantly enhanced fibroblast proliferation compared to the free form of the miRNA, reflecting the loading and delivery capacity of CPPs. In addition, the peptide coupling reaction promoted the coupling of peptides with metal complexes, and CPPs could be used as an efficient carrier for intracellular delivery of metal complexes [120]. For example, osmium (Os)(II)-bis(tetratoarginine) coupling achieves massive uptake and accumulation in a two-dimensional monolayer cell line and deep penetration into the cell membrane of a three-dimensional multicellular tumor spherical model of pancreatic cancer cells [121]. Obitz

Table 2
CPP-based drug delivery systems for cancer treatment.

Cell-penetrating peptides	Cargo	Targeted location	Ref
R3V6	SiRNA, BCNU	C6 glioblastoma	[116]
MGPE	Plasmid DNA	Human immortalized keratinocytes cell line HaCaT	[118]
YARA	MiR-21-5p	Mouse embryonic fibroblasts (MEFs)	[119]
Polyarginine	Os	Pancreatic Cancer Cells	[121]
Xentry TAT-9	Ru (II) bis(pyridinophenazine)	DNA	[122]
R8	Iridium (Ir)	NCI–H460 MCF-7	[123]
R9	DOX	Tumor-associated fibroblasts	[125]
TAT-A1	TAT-A1-GAPDH/siRNA	Human hepatocellular carcinomas HepG2	[127,128]
IMT-P8	KLA	Human cervical cancer cells HeLa	[129]
SCPP-PS	MTX	Human lung adenocarcinoma cells A549	[130]
ANG-TAT	PTX	Glioblastoma cells U87	[132]
ANG1005	PTX	Meningeal carcinoma cells U87MG	[133]
CPE_4 CPK_4	DOX	Skin epithelial cells	[134]
TAT	RLX	Human breast cancer cells MCF-7	[168]
NRPDSAQFWLHH	Hepatitis B VLNPs	Human squamous cell carcinoma cells A431	[169]
TAT-ETD	EDK	Human hepatocellular carcinomas HepG2 Human liver cancer cells Huh7	[170]

et al. [122]prepared the first ruthenium (Ru) (II) bipyridylphenazine biocouple by coupling a Ru (II) bipyridylphenazine complex with a non-polyarginine CPP Xentry peptide (LCLRPVG), and subsequently synthesized a biocouple enriched with arginine TAT-9 peptide on a resin, which can be applied to intracellularly-targeted imaging of cell nuclei and DNA. Gamba et al. [123] have successfully synthesized mono, di and trinuclear polypyridine iridium (Ir) (III)-octa-arginine polypeptide couplers (Ir-R8, Ir2-R8, and Ir3- R8) by using solid-phase peptide synthesis, which made Ir3- R8 one of the metal complexes-polypeptide couplers with the highest DNA affinity due to the high DNA-binding affinity of the polypeptide. In addition, Ir2-R8 was much more cytotoxic than Ir2 against NCI–H460 (lung cancer), MCF-7 (breast cancer), and A2780 cis (ovarian cancer) tumor cell lines, and Ir (III)-R8 organometallic polypeptide couplings inhibited cell survival by as much as 90% against the model adriamycin-resistant NCI/ADR-RES ovarian cell line. These Ir (III)-R8 had IC50 values in the same range as cisplatin and exhibited the same activity as cisplatin, suggesting that Ir (III)-R8 derivatives had promising clinical applications for the treatment of cancer.

Current evidence suggests that CPPs deliver therapeutic peptide ligands and proteins to the appropriate target sites in cancer cells [124], interacting with specific receptors within tumor cells to increase selectivity against tumor cells. For example, peptide nanocarriers constructed from cell-penetrating peptide R9 and cholesterol molecules can carry DOX; after surface modification with FAP-α antibodies, these nanocarriers bind to the surface antigens of CAFs and shed antibodies, enabling efficient drug penetration [125]. Vascular endothelial growth factor receptor-1 (VEGFR-1) is widely acknowledged to be an important protein for tumor cell growth [126]. Fang et al. [127,128] combined a tumor-targeting peptide A1 (WFLLTM) ligand with high affinity for VEGFR-1 screened from a phage library with TAT to form TAT-A1 complex CPPs. Compared with free TAT, the internalization rate of TAT-A1 on cells was significantly higher, and the internalization rate of human hepatocellular carcinoma cell HepG2 was increased by more than 50%. The study proved that TAT-A1 enhanced the penetration of HepG2 and inhibited the expression of VEGFR-1 for the treatment of hepatocellular carcinoma. Gautam et al. [129] prepared IMT-P8- KLA binding peptide by novel CPPs (IMT-P8) and pro-apoptotic peptide (KLA). A strong fluorescent signal in the mitochondria of HeLa human cervical cancer cells was observed after treatment with fluorescently-labeled IMT-P8-KLA, demonstrating the targeted delivery of KLA to the mitochondria and increased internalization of KLA in cancer cells. Besides, a substantial decrease in cellular viability was observed at a concentration of 20 μM IMT-P8-KLA using the MTT method, indicating that IMT-P8-KLA could induce apoptosis in cancer cells by targeting mitochondria.

DDSs composed of CPPs carrying chemotherapeutic drugs improve the penetration of the drugs into tumor cells. Yang et al. [130] reported selective CPPs functionalized multimers (SCPP-PS) with the sequence RLWMRWYSPRTRAYGC. The small size of CPPs (63 – 65 nm) enabled deep penetration into A549 cells. SCPP-PS achieved a 19.4 wt% loading of the anticancer drug methotrexate (MTX), completely inhibiting cancer cell survival activity. In A549 lung cancer mice injected with SCPP-PS-MTX for 8 h, accumulation in the tumor increased significantly, with 5.3% injectable dose/gram (ID/g). ANG-2 is a BBB-penetrating and activatable cell-penetrating peptide (ACPP) that targets low-density lipoprotein receptor-related protein 1 (LRP1), which is overproduced in brain tumors [131]. Li et al. [132] prepared ANG-TAT-PTX that could cross the BBB with the help of TAT. Brain uptake experiments demonstrated that ANG-TAT uptake in U87 glioblastoma cells was 1.8 times higher than ANG and 5.8 times higher than free PTX, improving the penetration of ANG and drugs into solid tumors. Besides, ANG-TAT-PTX treatment prolonged the survival rate of U87 homozygous mice for 15 days and attenuated U87 cell viability compared to PTX chemotherapy, providing a novel and highly effective DDS. In addition, a novel DDS (ANG1005) consisting of three PTX molecules covalently coupled to ANG-2 (ANG-PTX) was developed by Kumthekar et al. [133]. In a clinical trial involving adult patients with recurrent brain metastases from breast cancer (BCBM), ANG1005 demonstrated promising results. ANG1005 has been designed to break the enzyme cleavage linker and release PTX in response to LRP1 endocytosis. It was found that ANG1005 treatment resulted in stable control in 77% of intracranial and 86% of extracranial patients and was effective in treating BCBM disease. In this trial, 79% of patients in a subgroup of intracranial light meningeal carcinomas exhibited disease control with a mean overall survival of 8 months, highlighting its protective effect on the central nervous system of meningeal carcinoma patients. These research strategies optimized the therapeutic efficacy of DDSs based on CPPs and improved the concentration of chemotherapeutic agents at the target site. For effective delivery of therapeutic drug to living cells, Yang et al. [134] inserted a pair of complementary cholesterol- and PEG-modified coiled-coiled lipopeptides "E_4" [$(EIAALEK)_4$] and "K_4" [$(KIAALKE)_4$] into liposomes and into phospholipid bilayers targeting cell membranes, respectively. After in vitro cellular experiments and in vivo zebrafish embryo experiments, it was demonstrated that CPE_4/CPK_4 promoted the fusion of liposomes and targeting membranes, and at the same time rapidly released liposome-encapsulated fluorescent dyes and cytotoxic drug DOX. This strategy effectively improved the penetration ability of the drug into the cell and the efficiency of intracellular delivery, which provided the conditions for the rapid administration of the drug in the clinic and rapid release of the lipid drug in vivo, and effectively solved the problem of inefficient intracellular delivery of drugs due to the escape or degradation of the nuclear endosomes of lysosomes.

4. Peptide-based drug delivery systems responsive to various environmental stimuli

The tumor microenvironment refers to the internal and external environment that facilitates tumor growth and metastasis. It is influenced not only by the surrounding tissue structures but also by the interior environment of the cancer [135]. By responding to various endogenous TME stimuli (such as pH, enzymes, and redox potential) or exogenous stimuli (such as temperature, light, and heat), stimulus-responsive DDSs can undergo changes such as charge shift and size reduction, resulting in increased uptake and internalization by cancer cells (Fig. 2) [136]. This can enhance the targeted and penetrating delivery of drugs to malignant corpuscle, as well as improving the controlled liberation of drugs [137].

4.1. Enzyme-stimulated responsive peptide drug delivery system

Different types of overexpressed enzymes in diseased tissues can stimulate the induction of peptides [138]. When the concentration of extracellular enzymes such as MMPs and protein hydrolases is elevated in tumor tissues, it stimulates the response of peptide-based DDSs to control the release of anticancer drugs [139]. For example, histone protease B (cathepsin B, CTSB), highly expressed in the cytosol of bladder tumor cells, specifically recognizes the GFLG peptide and cleaves the peptide sequence between its F and L sites [140]. Zeng et al. [141] constructed a CTSB-responsive delivery system of a precursor drug (HCPT–FF–GFLG-EEYSA) based on bladder tumor-specific transforming peptides. The self-assembled peptide FF facilitated the formation of nanomicelles using the prodrug. The YSA (YSAYPDSVPMMS) peptide (Table 3) could target the EphA2 protein overexpressed outside the membrane of T24 human bladder cancer cells and enter the mouse tumor tissue. When exposed to CTSB, HCPT–FF–GFLG-EEYSA underwent cleavage and transformation into fibrous structures. Liquid chromatography-mass spectrometry (LC-MS) demonstrated that the CTSB-induced fibrous structure could slow the release of hydroxycamptothecin (HCPT), prolonging its efficacy and exhibiting the ability to prevent bladder tumor recurrence after surgery. Based on the relatively high protein hydrolase (FAP-α) activity on prostate CAFs, Ji et al. [142] designed FAP-α enzyme-responsive NPs based on the amphipathic substrate peptide CAP. TEM revealed that CAP could be assembled into ordered nanofibers and form spherical NPs after loading DOX. In the tumor environment of transplanted mouse human prostate cancer cells PC-3 and CAFs, CAP-DOX NPs were disassembled into disordered structures by FAP-α and rapidly released DOX within 3 h, which in turn enhanced the anticancer effect.

The peptide sequences extracted from enzyme cleavage substrates can be used as enzyme response motifs in DDSs, improving the sensitivity of the drug response. Wang et al. [143] co-assembled phospholipids and MRP, an amphipathic substrate for MMP-2 in pancreatic cancer tissues, to construct an MMP-2 enzyme-stimulated-responsive peptide-liposome hybrid nanocarrier (MRPL) that could carry the anti-fibrotic drug pirfenidone (PFD) and the anticancer drug gemcitabine. In this study, MMP-2 overexpression was

Table 3
Stimulus-responsive peptide-based DDSs for cancer treatment.

Stimuli-responsive peptides	Cargo	Targeted Tumor	Stimuli	Ref
YSA	HCPT	Human bladder metastatic cell carcinoma cells T24	CTSB	[141]
CAP	DOX	Human prostate cancer cells PC-3 and CAFs	FAP-α	[142]
MRP	PFD GEM	Pancreatic stellate cells (PSCs) Human pancreatic cancer cell line Mia-paca-2	MMP-2	[143]
GFFpY	LND	Human breast cancer cells HeLa	ALP	[144]
SPL	Prednisolone	Human colon adenocarcinoma cells LS 174T and Caco-2	pH	[148]
PEG-b-PLL/DMMA	PTX	Human breast cancer adriamycin-resistant cell line MCF-7/ADR	pH	[149]
Lan-PdNPs@GSH	DOX	Cervical cancer cells U14	Ph and laser	[150]
PTP-7	PTX	MCF-7, HCT116, 4T1	pH and Enzyme	[151]
OE	GEM PTX	Mouse breast cancer cells 4T1	Ph	[153]
KKFKFEFEF	MTX	Mouse breast cancer cells 4T1	Ph	[154]
SynB1-ELP	DOX PTX	Human breast adenocarcinoma cells MDA-MB 321	temperature	[158, 159]
RGD-ELP	DTX	Human breast adenocarcinoma cells MDA-MB 321	temperature	[160]
mPEG-b-PDTG	NR	Melanoma cells B16F10	ROS	[163]
Met-PEA-PEG	NR GA	Human Prostate cancer cells PC-3 Human cervical cancer cells HeLa	ROS	[164]
CPPT	Cur DOX	Human lung cancer cells A549	pH Reduction ROS	[166]
cRGD-rPTM	DOX	Human breast adenocarcinoma Cells MDA-MB 321	Reduction	[167]
PLA-b-PEG-b-pHis	DOX	Mammary tumor cell line MCF-7	pH	[171]
PE-pHis-PE-p(NIPAM)-FA-PC	DOX	Human oral epidermal-like carcinoma cells KB	pH and temperature	[172]
FA-PEG-b-PPLG	DOX	Folic acid high expression cancer cells KB	pH	[173]
PEG-b-PPLG NCA	DOX	Triple-negative breast cancer cell line MDA-MB-468	pH	[174]
PGlu	Antiangiogenic DNA	Mouse colon cancer cell CT26	pH	[175]
mPEsG-b-PEG-b-PLL/DOCA	DOX PTX	Human lung adenocarcinoma cells A549	pH	[176]
ELP (CP)	DOX	Mouse colon cancer cells C26	temperature	[177]
PEG-PLL/DMMA	Indocyanine Green (IGG)	Human cervical cancer cells HeLa	pH and Reduction	[178]
PEG_{114}-b-PLL_{25}/DMMA	DOX	Human lung adenocarcinoma cells A549	Reduction	[179]
PEG-PBnSec	DOX	Human cervical cancer cells HeLa	ROS	[180]

observed in rheumatoid mice implanted with pancreatic stellate fibroblasts (PSCs) and the human pancreas adenoma corpuscle line Mia-paca-2. Additionally, MRPL-PDF could facilitate PDF release in response to MMP-2 stimulation by the model drug rhodamine (Rhd). The MRPL component of the nanomicelle system enabled the targeted delivery of PFD to PSCs and downregulated ECM expression. Accordingly, MRPL-PDF enhanced the penetration of Rhd into pancreatic tumors to a depth of 972.2 ± 28.3 μm, 9.2 times higher than free MRPL, addressing the delivery barrier of gemcitabine and enhancing the efficacy of pancreatic cancer by inhibiting ECM secretion. Wu et al. [144] prepared a clonidine (LND)-GFFpY peptide coupling (sequence: LND-Gly-Phe-Phe-pTyr) using a standard solid-phase peptide synthesis method, which could be used as a cleavage substrate for alkaline phosphatase (ALP) after phosphorylation by Tyr(pY). During in vitro experiments, LND-GFFpY was dephosphorylated in ALP-overexpressing HepG2 hepatoma cells and self-assembled to form a fibrous network-like hydrogel LND-GFFY, demonstrating the gelation role of LND-GFFpY in cancer cells. LND-GFFpY released less than 5% of LND in buffer for 72 h, demonstrating the good stability of the covalent bond, while the release of LND under the influence of protease reached 28% and was proportional to the enzyme content, confirming the full liberation of the drug from this self-delivery system. The IC_{50} of LND-GFFpY in HepG2 cells was 146.8 μM, lower than that of the free LND team, indicating that LND-GFFpY had a stronger inhibitory effect on cancer cells in vitro. The IC_{50} value of LND-GFFpY increased 3.1-fold against normal cells compared to HepG2 cells, indicating the selective inhibitory effect of LND-GFFpY. In a mouse model of HeLa cancer cell transplantation tumors, LND-GFFpY reduced the density of tumor cells and caused tumor regression. Overall, this system could selectively deliver drugs spontaneously into cancer cells, catalyzed by phosphatases.

4.2. pH-stimulated responsive peptide drug delivery system

The pH-stimulated responsive peptide is a carrier molecule sensitive to an acidic environment, where lactic acid produced by high glycolysis of tumor cells and CO_2 produced by metabolism [145]result in a TCM pH between 6.5 and 7.2 [146]. This allows for efficient delivery and precise release of drugs from DDSs composed of pH-stimulated responsive peptides in the tumor microacidic environment [147], increasing the concentration of drugs at the target site. For example, poly (L-lysine) (PLL) can form pH-responsive peptide nanocarriers with different structures. In this respect, Nguyen et al. [148] prepared a 3-aminopropyl-functionalized mesoporous silica (MCM-NH2) coated with succinylated ε-PLL (SPL) NPs, demonstrating for the first time that SPL could release large amounts of prednisolone in low pH (pH 5.5–7.4) colonic epithelial cancer cells (LS 174T and Caco-2) with a loading of approximately 34% w/w for the diagnostic treatment of colon cancer. Huo et al. [149] prepared a charge reversal micelle (DA-NP) by encapsulating the P-glycoprotein (P-gp) inhibitor disulfiram (DSF) within the hydrophobic cores of a polyethylene glycol-block-poly-L-lysine (PEG-b-PLL) micelle with pH-responsive linkers dimethylmaleic anhydride (DMMA) and PTX attached to the L-lysine side chain. It was demonstrated that the zeta potential of DA-NPs remained at −1.5 ± 0.5 mV for 1 h at pH = 7.4, while at pH = 6.6, the zeta potential increased from −13.3 mV to 10.5 mV in 1.15 h. The surface charges of the coloaded DSF and PTX micelles were reversed from negative to positive, resulting in improved uptake by tumor cells. This change in surface charge facilitated the sequential release of both drugs within the tumor microenvironment. As a result, the inactivation of PTX on adriamycin-resistant human mammary tumor cells(MCF-7/ADR) was enhanced. DSF played a crucial role in restraining the transporter activity of P-gp, thereby improving the efficacy of PTX in overcoming drug resistance. Zhang et al. [150] synthesized palladium (Pd) nanoparticles (Lan-PdNPs) using the growth inhibitor analog lanreotide (Lan) as an internal template and assembled glutathione (GSH) on the surface of Lan-PdNPs. The negatively charged Lan-PdNPs@GSH formed a pH/photothermal dual-sensitive Lan-PdNPs@GSH/DOX nanosystem after adsorption of positively charged DOX under electrostatic gravitational force. The liberation of DOX in Lan-PdNPs@GSH/DOX was as high as 85.4% at a pH = 5.0 and upon irradiation with 808 nm IR laser in PBS buffer due to the low-acid conditions that disrupted the electrostatic reaction and accelerated release of DOX facilitated by the photothermal energy shift. In addition, the in vitro HeLa cancer cell activity was only 19.89%. In vivo studies showed that the Lan-PdNPs@GSH/DOX + laser irradiation group exhibited inhibition of transplanted cervical cancer cells in U14 tumor-bearing mice by up to 90.33%. In summary, Lan-PdNPs@GSH/DOX had good anti-cancer effects and the rate of production was much greater than chemotherapy and photothermolysis alone. This dual stimulation system increased the concentration and therapeutic intensity of the drug at the target site. In a study by Zheng et al. [151], the tumorolytic peptide PTP-7 was first bound to PEG via a peptide substrate of podoprotease to form mPEG-PTP-7 (PP) and then coupled PTX to the PTP-7 side chain via an acid-reactive amide bond (2-propionic acid-3-methylmaleic anhydride, CDM) to form PTP-7-PTX, which was further assembled into PPP NPs that produced a sequential response to dual Ph/podoprotease (legumain) stimulation. In an in vitro study, PPP released PTX faster in a pH 6.5 medium with an accumulation of 72.5% in 96 h, indicating that it could carry PTX to target microacidic tumor tissues, and enzymatic cleavage of PP could release PTP-7 and inhibit cancer cell growth. Compared to free PTX, PPP exhibited a higher inhibition rate of 4.8% in human mammary carcinoma cells MCF-7 spheroid tumors in vitro. In vivo studies showed that PPP reduced tumor volume by more than half in haploid mice with 4T1 podoproteinase-overexpressing breast cancer cells due to the acidic environment that breaks the CDM bond and releases PTX. The enzymatic activation of PTP-7 on cancer cells enhanced the therapeutic effect, providing a platform for the synchro delivery of anti-cancer drugs and active peptides to the tumor site.

Self-assembly of peptides to form hydrogels is promising in the fields of antitumor therapy and regenerative medicine, Lolita et al. [152]used nanotechnology to self-assemble peptide-based valsartan amphiphiles into a fibrous filamentous hydrogel structure, which accelerated the healing rate of diabetic wounds after topical administration of valsartan in diabetic rats, and had some therapeutic efficacy in diabetic wounds. Liu et al. [153] used a microwave synthesizer (CEM) to prepare a pH-sensitive OE (VKVKVOVK-VDPPT-KVEVKVKV-NH2) peptide hydrogel carrier. At specific concentrations and under physiological pH conditions, OE underwent self-assembly into nanofibrous structures, followed by assembly and cross-linking into three-dimensional network structures. During this process, OE was co-encapsulated with gemcitabine (GEM) and PTX. In an in vitro medium at pH 5.8, where

acidity disrupts the three-dimensional network structure, the total release of PTX and GEM from OE hydrogels reached 96.90% in 7 days and 99.99% in 3 days, respectively, indicating that OE hydrogels exhibited sustained drug release in an acidic environment. In vivo experiments on 4T1 tumor-bearing mice demonstrated that the group treated with the OE hydrogel carrying PTX and GEM exhibited a tumor inhibition rate of up to 90.84% after 7 days and reduced tumor weight of 0.19 g. In addition, there were no signs of injury or lesion in mice after subcutaneous injection of OE hydrogel. In summary, the OE hydrogel concentrated the release of GEM at the mammary tumor site in mice and then slowly released PTX, which prolonged the drug action time and enhanced the drug efficacy, with good biocompatibility in vivo, suggesting its huge prospects for application in the codelivery of multiple drugs. Zhang et al. [154] synthesized an injectable, pH-sensitive in situ self-assembled peptide-MTX hydrogel system by the classical solid-phase peptide synthesis (SPPS) method. MTX was coupled to the KKFKFEFEF peptide via a pH-responsive amide bond to form MTX-KKFKFEFEF(DA). In an in vitro study, the authors labeled KKFKFEFEF with fluorescein isothiocyanate (FITC) tracer for 6 h. DA (pH = 6.5) was efficiently taken up by three tumor cells and entered the lysosome via endocytosis, releasing MTX and exerting therapeutic effects under low pH stimulation. In vivo experiments in 4T1 tumor-bearing mice demonstrated that DA inhibited tumors up to 80 ± 0.78%. Furthermore, after H&E, TUNEL, and immunofluorescence Ki67 tumor staining section tissues, more necrotic tumor cells were observed in the DA-treated group, indicating that this system yielded a high inhibition rate on cancer cells under low pH stimulation and improved the efficacy of the drug in cancer.

4.3. Temperature stimulation-responsive peptide drug delivery system

External temperature stimuli can affect the ability of peptide carriers to control the release of anticancer drugs. It is now understood that elastin-like polypeptide (ELP) has temperature reversal properties. At the phase transition temperature (Tt), EPL is an irregularly curled helical structure, and when the temperature is higher than Tt, EPL will phase into a regular β-helix and can form a large hydrophobic polymer in the tumor vasculature. At temperatures below Tt, ELP undergoes a reversible structural transformation, dissolves in plasma, and forms a cross-concentration gradient inside and outside the blood vessels, facilitating the diffusion of ELP and accumulation in tumor tissues [155,156]. Therefore, ELP-based DDSs characterized by temperature stimulation responsiveness, biodegradability, and precise control have wide applications in cancer therapy and drug delivery [157]. Sonja et al. [158] designed a thermoresponsive biopolymer system, SynB1 ELP-DOXO, consisting of the cell-penetrating peptide SynB1, ELP, and a DOX (6-maleimidyl) hydrazone derivative (DOXO-EMCH), including a pH-sensitive hydrazone linker coupled to a tumor acidic lysosome capable of releasing DOX. The Tt of SynB1 ELP 1-DOXO was demonstrated to be 38 °C. The authors injected SynB1 ELP 1-DOXO into triple-negative human mammary tumor cells MDA-MB-231 allograft mice subjected to external heat therapy at a mild temperature of 41 °C for 2 h. Compared with the free DOX injection group, the uptake of DOX by cancer cells was 2-fold higher, DOX accumulation in the heart was 5-fold lower, and the tumor/heart accumulation ratio of ELP1-DOXO was 6-fold higher. In summary, this study illustrated the potential of ELP-based DDSs with thermoselective targeting, the ability to actively target tumor tissue and improve DOX accumulation under external temperature stimulation, and reduced DOX damage to cardiac tissue for the clinical treatment of breast cancer. Moreover, it has been reported that the SynB1-modified ELP-Notch coactivator MasterMind-Like1 (dnMAML) peptide coupling can form the heat-responsive peptide vector SynB1-ELP1-dnMAML. The Notch signaling pathway promotes the hyperplasia and differentiation of tumor stem cells (CSCs). Therefore, blocking the Notch signaling pathway in the tumor is key to preventing cancer recurrence. Robinson et al. [159] observed the sustained accumulation of SynB1-ELP1-dnMAML for 42 h at the tumor site of MDA-MB-231 tumor-bearing mice after intravenous injection of SynB1-ELP1-dnMAML followed by local thermotherapy at an external temperature of 40-41 °C, which prolonged the half-life of the dnMAML peptide. In addition, SynB1-ELP1-dnMAML-PTX combination treatment inhibited tumor growth by 72% at day 26, reducing cancer cell resistance. In summary, ELP combined with local thermotherapy actively targets tumor tissue and enhances the efficacy of PTX by blocking the Notch signaling pathway, and PTX combination therapy is expected to prevent the occurrence of recurrent breast cancer. This suggests that ELPs can promote the internalization of drugs by tumor corpuscle, slowing drug release and prolonging drug efficacy.

Vallejo et al. [160] developed novel nano-DDSs using supercritical fluid (SCF) technology and supercritical antisolvent (SAS) technology to encapsulate the chemotherapeutic agent DTX in RGD-modified genetically engineered elastin recombinants (ELRs). ELRs exhibited temperature reversal and could decompose into stable NPs with a particle size of 40 nm, improving DTX water solubility. It was demonstrated that the release rate of ELRs-DTX NPs in tumor cells gradually slowed down after 10 h until complete release at 96 h. 1 mM ELRs-DTX NPs completely inhibited the hyperplasia of MDA-MB-231. Combined with the tumor-targeting peptide RGD, they demonstrated enhanced inhibition against mammary carcinoma cells, paving the way for a novel controlled release system.

4.4. Redox stimuli-responsive peptide drug delivery system

Redox-stimulated-responsive peptides are designed to be responsive to the redox potential in the TME, determined by the levels of reactive oxygen species (ROS) and GSH disulfide bond concentration. These peptides can be harnessed to build nanodrug delivery systems triggered by changes in ROS and GSH differences [161] to achieve drug release and aggregation at specific sites with significant colloidal stability.

4.4.1. Oxidative stimulation

ROS mainly contain hydrogen peroxide (H_2O_2), superoxide ($O_2\bullet^-$), and hydroxyl radicals (•OH) [162]. When redox reactions occur between thioether-containing peptides and ROS, the hydrophobic thioether group is oxidized to hydrophobic sulphoxide groups,

leading to the cleavage of the thioether peptide-based DDS and the release of therapeutic drugs. Zhang et al. [163] prepared the amphiphilic polypeptide-based block copolymer mPEG-b-PDTG, a new ROS-sensitive DDS containing 1,4-dithioamino-glutamic acid amino-carboxymethyl hydride (DTG-NCA), by ring-opening polymerization (ROP) of 1,4-dithioamino-glutamic acid amino-carboxymethyl hydride. The experiments showed that mPEG-b-PDTG self-assembled into nanomicelles in solution, and after treatment with 100 mmol/L H_2O_2, the micelle size gradually decreased to 40 nm, and the rate of size reduction was proportional to the H_2O_2 concentration, demonstrating the ROS-inductive behavior of mPEG-b-PDTG. Next, the authors loaded the model drug Nile Red (NR) onto mPEG-b-PDTG and found that the NR release rate was proportional to the H_2O_2 concentration, as demonstrated by dynamic light scattering (DLS) and turbidity measurements, which was due to H_2O_2 cleavage of micelles. In summary, mPEG-b-PDTG provides a platform for ROS-responsive DDSs. In addition, Xu et al. [164]synthesized a thioether-based peptide polymer Met-PEA-PEG responsive to ROS. Met-PEA-PEG is an amphiphilic polymer that couples a hydrophilic PEG shell to a hydrophobic L-methionine polyester amide (Met-PEA) and can self-assemble into micellar NPs. It was demonstrated that the release of Met-PEA-PEG was dependent on the H_2O_2 concentration of Nile red dye and exhibited sensitivity to high levels of ROS in PC3 prostate cancer cells. Besides, Met-PEA-PEG NPs carrying gambogic acid (GA) showed high cytotoxicity against HeLa cancer cells, improving GA's efficacy. Accordingly, they represent a promising system for targeted anticancer drug delivery.

4.4.2. Reduction of stimulation

In the tumor microenvironment, GSH is the main reducing substance attached to disulfide bonds in the side chains, which can be bound to peptide nanocarriers to form cross-linked NPs. Under highly reducing conditions, the disulfide bonds are reduced to sulfhydryl groups and broken, releasing the disulfide-containing peptide carriers with loaded therapeutic substances [165]. For example, Li et al. [166] synthesized a novel polypeptide disulfide cross-linked methoxy polyethylene glycol-polyaspartate-tyrosine CPPT, which loads curcumin (Cur) in a hydrophobic core and loads DOX hydrochloride on the hydrophilic segment and calcium phosphate (CaP) shell to form pH/redox dual-sensitive CPPT@CaP-CD NPs. As shown by in vitro cellular experiments, rapid dissolution of CaP shells and disulfide bond breaking occurred under acidic conditions of tumors with low oxygen and high concentrations of GSH, which released drugs and had a highly toxic effect on human lung cancer cells A549. This organic-inorganic vector facilitated the development of combination drugs. Song et al. [167] prepared reduction-sensitive poly(ethylene glycol)-b-poly(l-tyrosine)-lipoic acid (PEG-b-PTyr-LA)-based poly(ethylene glycol)-b-poly(l-tyrosine)-lipoic acid (cRGD-rPTM) cross-linked micelles (cRGD) modified by targeting peptide cRGD. In vitro experiments showed that cRGD-rPTM had a DOX charging ability of more than 90% in the presence of the antioxidant LA, improving drug loading and targeting cancer cells. After intravenous injection of cRGD-rPTM into MDA-MB-231 tumor-bearing mice, the mice showed a high accumulation of DOX. The micellar disulfide bonds within the system were susceptible to cleavage by cytosolic glutathione (GSH), leading to the controlled release of DOX. This mechanism resulted in a remarkable inhibition of mammary tumors, with a reduction in tumor size of up to 84.2%. Taken together, cRGD-rPTM indicates that cRGD-rPTM is an effective nanoplatform for targeted chemotherapy.

5. Conclusion and future prospects

This paper reviews the research progress of functional peptide-based DDSs at home and abroad, and specifically introduces the targeting receptors of CTPs, the uptake pathways of CPPs and the conditions of induction of different stimulus-response peptides by the endogenous environment of TME, as well as the therapeutic prospects of DDSs composed of these peptides for diseases such as tumors. DDSs consisting of the peptides described in the above sections have been extensively studied in corpore and in vivo, but there is a relative paucity of clinical practice studies. In addition, peptide-based clinical therapies only exert the therapeutic effect of the peptide drug itself, rather than acting as a delivery system to treat the diseases. This requires further research to address this issue. In addition, peptide-based clinical therapies only exert the therapeutic effect of the peptide drug itself, rather than acting as a delivery system to treat the diseases. This requires further research to address this issue.

Compared with single chemotherapy drugs and antibody-drug conjugates, PDCs are novel peptide-based DDSs with the advantages of small size, high bioavailability, and easy penetration of biological membranes [181]. Peptides have primary effect in DDSs, and the targeting and penetrating nature of peptides are key attributes for the precise delivery of drugs to the location of lesions. To treat complex tumor diseases, peptide-based DDSs can adapt to the complex environmental changes of tumors and target the tumor microenvironment to give full play to the structural characteristics and biological effects of peptide molecules. However, the technology for synthesizing higher stability peptides coupled in PDCs is a challenge that needs to be overcome. In the future, PDCs technology will be an emerging R&D hotspot with tumor-specific targets and endocytosis targets as dual targets to achieve bifunctional combination, but there are also many "hard bones" that need to be overcome, such as clinical application problems.

In the past two years, with the market demand for bifunctional peptides Pegcetacoplan (APL-2) and Tirzepatide [182,183], the development of peptide drug carriers has been promoted, which provides a favorable environment for targeted drug delivery to specific sites and opportunities for more peptide drugs to be used in clinical treatment. The successful launch of semaglutide tablets and octreotide capsules demonstrates that oral delivery of peptide-active drugs is feasible. When transmembrane effects in the gastrointestinal tract can be combined with some form of PDCs, DDSs will provide multiple opportunities for biopharmaceutical applications [24]. For example, Tao et al. [184]used the edible cyanobacterium *Spirulina platensis* as a drug delivery carrier, which can effectively adhere to the intestinal wall, and has good bio-compatibility after loading the drug curcumin, which can effectively prolong the action time of the drug in the intestinal tract and reach up to 60 days, and the tumour growth inhibition rate is 88.7% [185], which is able to cope with the therapeutic challenges of intestinal diseases, and is an innovative means of oral drug delivery. Achieving precise control over peptide self-assembly is crucial in enhancing drug delivery outcomes. Comprehensive studies on the impact of internal and

external environmental stimuli on peptides are necessary. Indeed, by understanding and adapting to the conditions present at the site of the lesion, we can optimize the delivery of drugs and improve their efficacy.

Whether peptide-based DDSs self-assemble to form NPs or bind to other NPs to form complexes, peptide carriers have shown excellent therapeutic promise in improving the efficacy of diseases such as cancer. However, it should be borne in mind that peptide-based DDSs also present certain challenges, such as a short half-life of in vivo circulation, more reactive sites for peptides, and difficulty in controlling the size of self-assembled peptide infrastructures. In addition, there are various bottlenecks in oral drug delivery, including limited number of drugs administered, degradation by oral and gastrointestinal enzymes, and inefficient controlled drug release. Bioinspired oral drug delivery devices ameliorate the above problems to some extent, for example, antimicrobial peptides isolated from royal jelly can be self-assembled into a hydrogel system as an anti-infective bioinspired oral drug delivery devices [186]. However, there are still disadvantages such as the inability to interact autonomously with the gastrointestinal environment, incomplete drug therapeutics, and insufficient clinical trials. 4D printing technology can optimize the processing of bioinspired oral drug delivery devices, but balancing the printing resolution and bioactivity of living components, and high-throughput printing of multiple biomaterials remain challenging [187]. In the future, addressing these challenges will be a primary focus and a significant hurdle to overcome to enhance the capabilities of peptides. Improving drug efficiency and pharmaceutics is the fundamental goal of drug delivery systems, and the coupling of peptides and drugs will improve the efficacy and pharmaceutics because of this, the development of peptides holds great promise. Ultimately, We can combine the knowledge of genomics technology, information technology and disease biology with the development of peptide-based DDSs to create specific targeting peptides and precise self-assembling peptides. The DDSs based on bi-functional peptides can be rationally designed for similar targets or different targets of the same disease to achieve drug delivery by combining peptides and thus play a synergistic role. The vigorous development of peptide-based DDSs will contribute to the advancement of healthcare and benefit mankind.

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Data availability statement

No data was used for the research described in the article. Data associated with the study has not been deposited into a publicly available repository.

CRediT authorship contribution statement

Sijie Guo: Writing – original draft, Conceptualization. **Jing Wang:** Writing – original draft, Investigation. **Qi Wang:** Writing – original draft, Investigation. **Jinxin Wang:** Writing – original draft, Investigation. **Song Qin:** Writing – original draft, Investigation. **Wenjun Li:** Writing – review & editing, Supervision.

Declaration of competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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