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Review article

Peptide-decorated polymeric nanomedicines for precision cancer therapy

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ABSTRACT

The advancement of tissue and cell-specific drug delivery systems is a key to precision cancer therapy. Peptides, with easy synthesis, low immunogenicity and biological functions closely mimicking or surpassing natural proteins, have been actively engineered and explored to provide nanomedicines with the ability to overcome various extracellular and intracellular delivery barriers ranging from phagocytic clearance in the circulation, low tumor penetration, poor cancer cell selectivity, inferior cell penetration, to endosomal entrapment as well as poor blood brain barrier permeation for brain cancer therapy. Anti-tumor studies with peptide-decorated polymeric nanomedicines are currently in the experimental stage. Most of the reported peptide-directed polymeric nanomedicines do have a rather complex design requiring a multi-step reproducible fabrication process. Moreover, many of the proposed peptide-decorated polymeric nanomedicines are still not able to effectively overcome the drug delivery cascade barriers. Consequently, in order to facilitate clinical translation the complexity of the systems has to be reduced, while maintaining the added functions after the introduction of the different peptides and further progress has to be made in passing the various drug delivery barriers. In this review, we give an overview of the rational design, development and preclinical performance of peptide-decorated polymeric nanomedicines, and further discuss their challenges and future perspectives as a next generation cancer treatment modality.

Abbreviations: AF, aminoflavone; ANG, angiopep-2; BBB, blood brain barrier; BCECs, brain capillary endothelial cells; BP, bortezomib-pinanediol; bPEISS, bioreducible branched polyethylenimine; BPLP, biodegradable photo-luminescent polymer; CA, cholic acids; CDDP, cisplatin; Ce6, chlorin e6; CPP, cell penetration peptides; CPT-11, Irinotecan hydrochloride; CS, chitosan; DA, 2,3-dimethylmaleic anhydride; DACHPt, 1,2-diaminocylohexane platinum(II); DDP*, cisplatin resistant; DEPt, dendrimer encapsulating platinum nanoparticles; DET, diethylenetriamine; DM1, mertansine; DOX, doxorubicin; DOX·HCl, doxorubicin hydrochloride; DSPE, 1,2-distearoyl-sn-glycero-3-phosphoethanol-amine; EGFR, epidermal growth factor receptor; EPI, epirubicin; GA, gambogic acid; FGFR, fibroblast growth factor receptors; GrB, granzyme B; GSH, glutathione; HA, hyaluronic acid; HIFU, high-intensity focused ultrasound; Hsp90, heat shock protein 90; HSV-TK, herpes simplex virus type I thymidine kinase gene; ICG, Indocyanine green; i.p., intraperitoneal; LDLR, low-density lipoprotein receptor; LHRHR, luteinizing hormone-releasing hormone receptor; Lin, linoleic acid; LND, lonidamine; LNM, lymph node metastatic; LRP1, low-density lipoprotein receptor-related protein-1; -Luc, luciferase expressing; Mal-SH, maleimide-thiol; MDGF, mammary-derived growth factor; MMP-2, matrix metalloproteinase 2; MPA, 1-(3-mercaptopropyl)amidine; nAChR, nicotinic acetylcholine receptor; NIS-cDNA, sodium iodide symporter complementary DNA; NPs, nanoparticles; NRP-1, neuropilin-1; o.t., orthotopic; PAMAM, polyamidoamine; PAPBA, poly(N-3-acrylamidophenylboronic acid); PAsp, polyaspartamide; Pc 4, silicon phthalocyanine-4; PCC-*g*-GEM/DC, poly(2-methyl-2-carboxyl-propylene carbonate)-*g*-gemcitabine/dodecanol; PCL, poly(ε-caprolactone); PDMA, poly(2-(dimethylamino) ethyl methacrylate); PDPA, poly(2-(diisopropylamino) ethyl methacrylate); PDSEMA, poly(pyridyl disulfide ethyl methacrylate); PDTC, poly(dithiolane trimethylene carbonate); PE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; PEG, poly(ethylene glycol); PEGMA, poly(ethylene glycol)methyl ether methacrylate; PFOB, perfluorooctyl bromide; PGlu, poly(L-glutamic acid); P(HCPT/DTDE), poly(dithiodiethanol-alt-10-hydroxycamptothecin); PHEP, poly(2-hexoxy-2-oxo-1,3,2-dioxaphospholane); PHis, poly(L-histidine); PHPMA, poly(N-(2-hydroxypropyl)-methacrylamide); PLA, poly(D,L-lactic acid); PLGA, poly(D,L-lactide-*co*-glycolide); PLL, poly(L-lysine); POEGMA, poly(oligoethylene glycol methacrylate); pOEI, poly(branched oligoethylenimine); pORF-TRAIL, therapeutic gene encoding human tumor necrosis factor-related apoptosis-inducing ligand; PPa, pyropheophorbide-a; PTMBPEC, poly(2,4,6-trimethoxy benzylidenepentaerythritol carbonate); PTX, paclitaxel; R9, nona-arginine; RNAi, RNA interference; SAL, salinomycin; s.c., subcutaneous; SHH, human sonic hedgehog; siLuc, the siRNA against the firefly luciferase gene; siPLK1, Polo-like kinase1 specific siRNA; SN38, 7-ethyl-10-hydroxy-camptothecin; TMC, trimethylene carbonate; TPGS, D-α-tocopherol polyethylene glycol succinate; TPZ, tirapazamine; TS, D-α-tocopheryl succinate; TTMA, 2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl) ethane methacrylate; uPAR, urokinase plasminogen activator receptor; VAN, vandetanib

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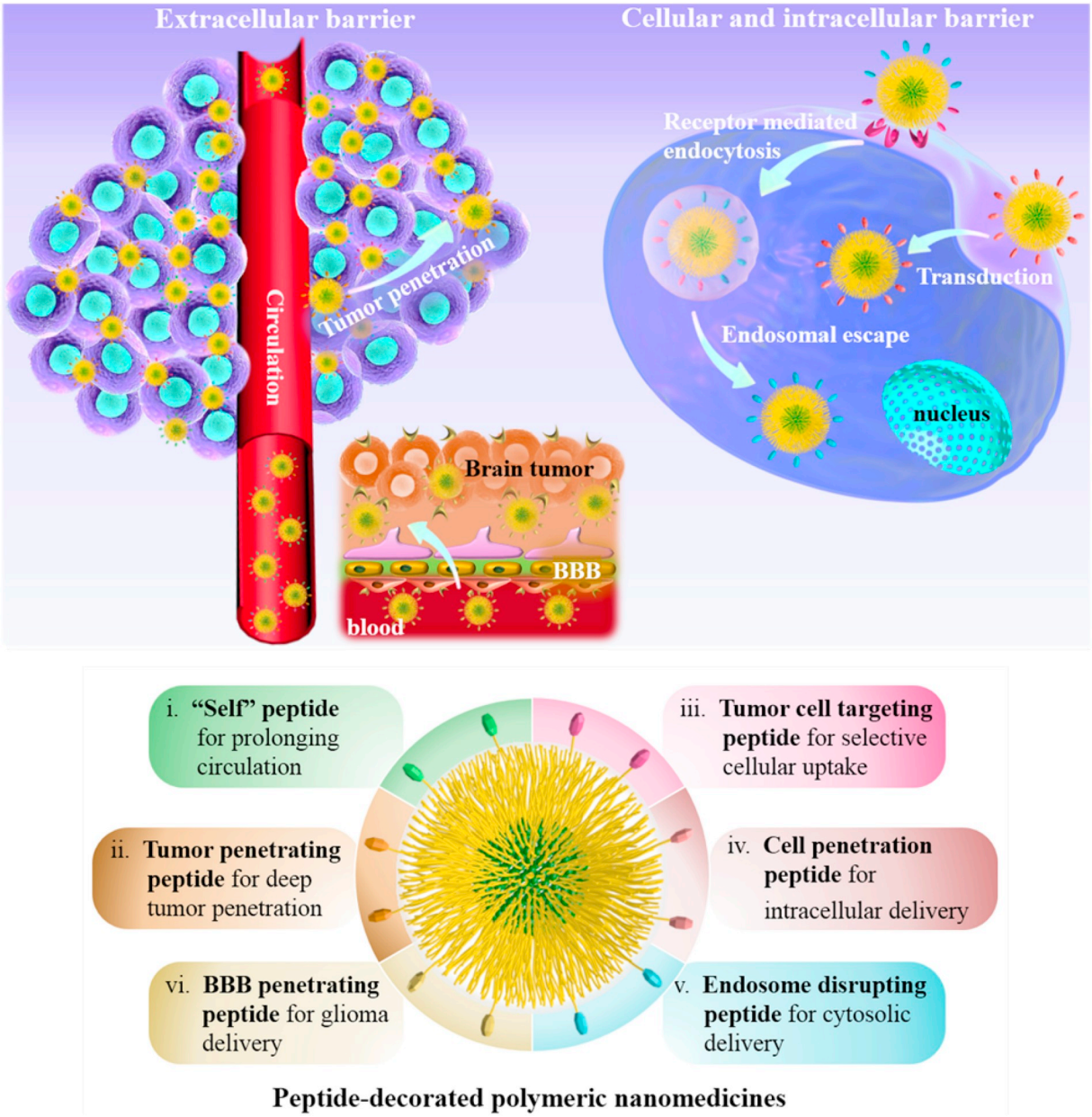
1. Introduction

Cancer is one of the leading causes of death in the world. Polymeric nanomedicines have emerged as a promising platform for the treatment of malignant tumors over the past decades [1–4]. Polymeric drug carriers, including polymeric micelles [5,6], polymersomes [7,8] and nanogels [9,10], in general can improve the stability, prolong the circulation time, reduce side effects, enhance tumor accumulation by passive targeting, and potentially control the release of bioactive therapeutics [11–14]. Another important benefit of using polymeric drug carriers derives from their versatility in tuning the physicochemical properties and accommodation of a range of payloads from anticancer drugs to proteins and genes [15,16]. Despite these advantages, the pre-clinical progress and outcome of systemically delivered polymeric nanomedicines remain unsatisfactory and at least five important challenges have to be addressed. These include: (i) short circulation times because of uptake by the reticuloendothelial system; (ii) low tumor accumulation (~0.7% of injected dose) as a result of fast clearance from the circulation and poor vascular extravasation; (iii) poor tumor penetration due to the presence of a high interstitial fluid pressure and dense extracellular matrix; (iv) inferior tumor cell uptake due to stealthy PEG coatings; and (v) inefficient cytosolic drug release owing to the entrapment in acidic endosomal/lysosomal compartments [17–19]. In order to overcome these five bottlenecks in the drug delivery cascade and achieve high antitumor efficacy, thousands of functional polymeric nanosystems have been engineered in the past decades [20–22]. For instance, particles have been modulated with respect to size (small), non-spherical shape, different ligands (e.g., antibody, aptamer) and/or protonatable groups to improve their tumor penetration, cellular uptake and/or endosomal escape [23–25].

Peptides, with good stability, low cost, ease of manipulation, large-scale production and diverse functions, provide a unique tool in guiding polymeric nanomedicines to accomplish the drug delivery cascade from circulation, tumor accumulation and penetration, to tumor cell



Scheme 1. Emerging peptide-decorated polymeric nanomedicines with the ability to overcome various extracellular and intracellular delivery barriers ranging from phagocytic clearance in the circulation, low tumor penetration, poor cancer cell selectivity, inferior cell penetration, to endosomal entrapment for tumor therapy, as well as poor blood brain barrier permeation for glioma therapy.

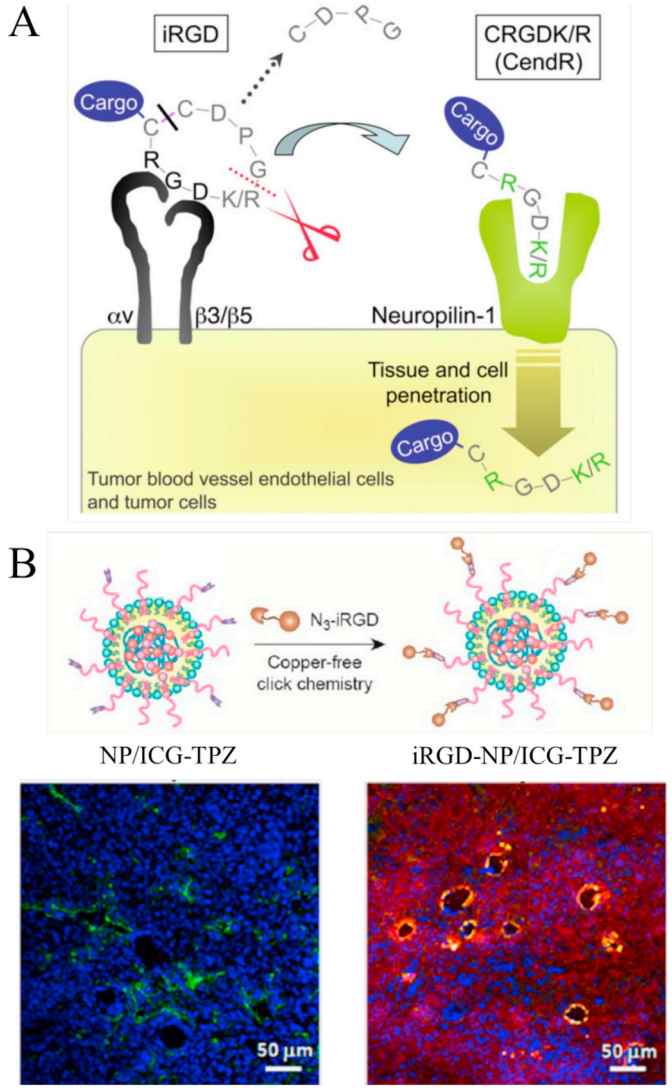


Fig. 1. (A) Tumor tissue homing and penetration mechanism of iRGD peptide [44]. (B) Confocal images of a tumor section showing the tumor penetration of ICG and TPZ co-loaded PLGA/DSPE-PEG nanoparticles (NP/ICG-TPZ) and iRGD-NP/ICG-TPZ (green: blood vessels, blue: cell nucleus, red: ICG) in orthotopic 4T1 tumor-bearing Balb/c mice [52]. Reproduced with permissions from refs [44,52].

internalization and cytosolic drug release for improved tumor therapy [26–28]. Up to now, peptides with different functionalities varying from self-identity [29], tumor penetration [30–32], cell targeting and/or penetration [33], endosomal escape and blood brain barrier (BBB) crossing [34,35] have been introduced onto polymeric nanocarriers by robust chemical strategies. The impacts of functional peptide installation on the biological performance of polymeric nanomedicines are illustrated in Scheme 1. These peptide-decorated nanosystems have demonstrated prolonged circulation, enhanced tumor accumulation and penetration, improved cellular uptake, and/or effective cytosolic drug release to treat tumors with high efficiency both *in vitro* and *in vivo*. In this review, we will discuss the progress in the field of peptide–decorated polymeric nanomedicines for improved tumor therapy over the last seven years. Systems decorated with peptides will be classified by the function of the peptides namely self-identity, tumor penetration, targeting, cell penetration, endosomal escape and permeation of the BBB. The details regarding peptide sequence and conjugate chemistry, as well as types of polymeric nanocarriers, drugs and in *vitro* and *in vivo* tumor models will be presented.

2. "Self" peptide for prolonging circulation

For systemically administered polymeric nanomedicines, the longer the systems persist in the circulation, the higher the possibility of accumulation in the tumor. Therefore, avoiding rapid *in vivo* clearance is one of the major challenges for developing nanomedicines [36]. Surface PEGylation has been a widely developed strategy to delay phagocytic clearance and consequently extending the circulation time of nanocarriers to some degree [37,38]. However, PEGylation inevitably raises several issues such as hindering cellular uptake and endosomal escape of nanomedicines, as well as activation of the complement system triggering accelerated blood clearance after repeated injections [39,40]. Other alternatives to improve the circulation time of nanoparticles are just emerging. Recently, Disher's group designed and synthesized a 21-amino acid "self" peptide (GNYTCEVTELTREGETIIELK) by minimization of human CD47, which can interact with signal regulatory protein-α (SIRPα) on macrophages to inhibit phagocytic uptake and *in vivo* clearance [29]. It was demonstrated that "self" peptide decorated polystyrene nanoparticles had a much higher persistence ratio and prolonged circulation time compared to that of scrambled peptide or poly(ethylene glycol) (PEG) modified particles in NSG mice, wherein, persistence ratio doubling times of 20, > 75 and > 200 min were observed, respectively. Consequently, "self" peptide enhanced the delivery of particles to the tumor site by 16-fold and improved the anti-tumor efficacy of paclitaxel (PTX)-loaded particles. This "self" strategy works well for nanomedicines following systemic administration with significantly prolonged circulation and enhanced tumor accumulation as compared to PEGylation. It should be noted, however, that the design and engineering of the nanomedicines with self-peptide may be rather complicated. In principle the surface chemistry of the systems will be altered and possibly also their stability.

3. Tumor penetrating peptide for promoting deep tumor penetration

Most solid tumors have an elevated interstitial fluid pressure and a dense extracellular matrix that directly limit the transportation of accumulated polymeric nanomedicines, which generally locate nearby the tumor vessels and are inaccessible to deep tumor tissue [17]. Such poor tumor penetration stands as one of the most important issues for nanomedicines, resulting in drug resistance and limited therapeutic efficacy [41,42]. Recently, peptides containing the CendR motif (R/KXXR/K) were found to activate the trans-tissue pathway by binding to the neuropilin-1 (NRP-1) receptor, overexpressed by vascular endothelial cells, tumor cells and various other cell types at the tumor site, thus triggering the vascular and tissue penetrability of nanomedicines [43–45]. Apart from the CendR motif, these peptides also contain the targeting unit for tumor specific homing. Cyclic iRGD with a sequence of c(CRGDKGPDC), is taken as an example to illustrate the tumor targeting and penetration mechanism: (i) iRGD specifically binds to αv integrins that are expressed on tumor endothelium through the RGD motif; (ii) iRGD is cleaved by proteases at the tumor site to produce the fragment CRGDK which contains a CendR motif; (iii) CRGDK binds to NRP-1 inducing tissue penetration (Fig. 1A) [43,44].

iRGD and other tumor penetrating peptides such as iNGR and tLyP-1, have been decorated on the surface of polymeric nanomedicines for the treatment of a range of subcutaneous and orthotopic tumor models (Table 1). For example, iRGD was incorporated into PEGylated polyamidoamine (PAMAM) dendrimer doxorubicin (PAMAM-PEG/DOX) conjugates by maleimide-thiol (Mal-SH) michael addition [46]. The resulting iRGD-functionalized conjugates showed similar *in vitro* cellular uptake and cytotoxicity to C6 glioma cells as those decorated with c(RGDyC), likely because they share the same targeting procedure. However, *in vivo* studies showed that iRGD conjugates had higher accumulation and deeper penetration in orthotopic C6 glioma, thus achieving longer survival times compared to the c(RGDyC) system.

Table 1
Tumor penetrating peptide modified polymeric nanomedicines used for tumor treatment.

Peptide	Sequence	Conjugate chemistry	Nanocarriers	Drug	Tumor model		Ref.
					In vitro	*In vivo*	
iRGD	Cc(CRGDKGPDC)	Mal-SH	PAMAM-PEG/DOX conjugates	DOX	C6	o.t. C6	[46]
		Mal-SH	POEGMA-PDPA Ps	PTX/ DOX	PPC-1, M21, MKN-45P, CT26	i.p. and s.c. MKN-45P & CT26	[47]
		Mal-SH	PEG-PLA NPs	VAN	BEL-7402, HepG2, HuH-7, HCC-LM3	s.c. BEL-7402	[48]
	CRGDKGPDC	Mal-SH	PEG-DSPE Ms	SAL	HepG2	s.c. HepG2	[49]
		Mal-SH	CS-PAPBA NPs	DOX	SH-SY5Y	s.c. H22	[50]
	c(CRGDKGPDC)	amidation	PHPMA-DOX prodrugs	DOX	DU-145	–	[51]
	N_3-c(CRGDKGPDC)	click chemistry	DSPE-PEG/PLA NPs	ICG & TPZ	4T1	o.t. 4T1	[52]
	c(CRGDKRGPDEC)	Mal-SH	PEGMA-PDPA –PDMA	siLuc	A549-Luc	s.c. A549-Luc	[53]
iNGR	c(CRNGRGPDC)	amidation	PEG-PLGA NPs	PTX	U87MG	o.t. U87MG	[54]
iNGR iNGRt	c(CRNGRGPDC) CRNGR	amidation	pOEI-PEG NPs	RNAi	U87MG, HUVEC	o.t. U87MG	[55]
iRGDt	CRGDK	Mal-SH	PEG-DSPE capsules	CPT-11	HT-29, HUVEC, MCF-7	s.c. HT-29	[56]
		Mal-SH	PEG-DSPE Ms	DOX	MDA-MB-231, MCF-7	s.c. MDA-MB-231	[57]
tLyp-1	CGNKRTR	Mal-SH	HATS/PEG-TS NPs	DTX	PC-3, MDA-MB-231, 4T1	s.c. PC-3, metastasis MDA-MB-231, o.t. 4T1	[58,59]
		Mal-SH	PEG-PLA NPs	PTX	C6	o.t. C6	[60]
F3	CKDEPQRRSARLSAKPAPPKPEPKPKKAPAKK	Mal-SH	PPa-PLA-PEG-PLA-PPa NPs	PTX & PPa	HCT-15, HUVEC	s.c. HCT-15	[61]
		Mal-SH	PEG-PLA NPs	PTX	C6	o.t. C6	[62]
AC	CGKRKGYGATWLPPR	Mal-SH	PEG-PLA NPs	PTX	U87MG, HUVEC	o.t. U87MG	[63]

Note: o.t., orthotopic; Ps, polymersomes; NPs, nanoparticles; Ms, micelles; s.c., subcutaneous; CS, chitosan; CPT-11, Irinotecan hydrochloride; PPa, pyropheophorbide-a.

iRGD-tethered poly(oligoethylene glycol methacrylate)-*b*-poly(2-(diisopropylamino) ethyl methacrylate) (POEGMA-PDPA) polymersomes with encapsulated PTX showed a higher toxicity to NRP-1 positive PPC-1 prostatic cells than to NRP-1 negative M21 melanoma cells [47]. Furthermore, enhanced tumor selective accumulation and penetration was observed for these polymersomes in both subcutaneous and intraperitoneal MKN-45P gastric and CT-26 colon tumor models as compared to naked polymersomes, thus leading to improved antitumor efficacy. Significantly improved therapeutic effects in subcutaneous liver tumor-bearing mice were also observed for iRGD–decorated vandetanib (VAN) containing PEG-*b*-poly(D,L-lactic acid) (PEG-PLA) nanoparticles, salinomycin (SAL)-loaded PEG-DSPE (DSPE: 1,2-distearoyl-sn-glycero-3-phosphoethanol-amine) micelles, and DOX-loaded chitosan-poly(N-3-acrylamidophenylboronic acid) (CS-PAPBA) nanoparticles compared to their corresponding non-modified counterparts [48–50]. As a result of iRGD-promoted tumor homing and matrix metalloproteinase 2 (MMP-2) induced release of free iRGD to regain its penetration ability, MMP-2-sensitive poly(N-(2-hydroxypropyl)-methacrylamide)-DOX/iRGD (PHPMA-DOX/iRGD) conjugates demonstrated a higher toxicity to DU-145 prostate cancer cells and higher penetration in 3D DU-145 tumor cell spheroids than PHPMA-DOX conjugates [51]. Zhou and Oupický's group developed hybrid PLGA/DSPE-PEG (PLGA: poly(D,L-lactide-*co*-glycolide)) nanoparticles for simultaneous loading of Indocyanine green (ICG) and tirapazamine (TPZ) to achieve photodynamic and hypoxia activated chemotherapy [52]. These nanoparticles, upon installation of iRGD via copper-free click chemistry, showed significantly deeper penetration in an orthotopic 4T1 tumor (Fig. 1B), which resulted in nearly complete elimination of the tumor in 13 days. Furthermore, iRGD-decorated siLuc (siRNA against the firefly luciferase gene) polyplexes based on poly(ethylene glycol)methyl ether methacrylate-*b*-PDPA-*b*-poly(2-(dimethylamino) ethyl methacrylate) (PEGMA-PDPA-PDMA) triblock copolymer efficiently down regulated the luciferase expression of subcutaneous luciferase expressing A549 (A549-Luc) lung tumor-bearing nude mice by 91.67% compared to polyplexes without iRGD peptide [53].

iNGR with a sequence of c(CRNGRGPDC), acts similarly to iRGD with sequential binding to aminopeptidase N (APN), cleavage to CRNGR containing a CendR motif that binds to NRP-1 enhancing tissue penetration. The introduction of iNGR peptide to PEG-PLGA nanoparticles significantly lengthened their travel distance after extravasation from blood vessels [54]. As a result, PTX-loaded iNGR-tethered nanoparticles induced longer survival in orthotopic U87MG glioma-bearing nude mice than PTX-loaded PEG-PLGA nanoparticles, with median survival times of 43 versus 27 days. Jiang and co-authors reported that redox-sensitive iNGR-PEG-pOEI (poly(branched oligoethylenimine)) polycations could condense RNA interference (RNAi) nanospheres into compact nanoparticles with a size of ~90 nm [55]. The nanoparticles accumulated distinctly more in orthotopic U87 glioma than the non-targeting control. Therefore, remarkably down regulated tumor luciferase up to several fold lower was observed as a result of the sequential release of RNAi nanospheres and siRNA upon entering into glioma cells with high concentrations of glutathione (GSH) and enzyme (e.g. dicer, a member of the RNase III family). Additionally, the truncated forms of iRGD and iNGR have also been demonstrated to afford drug or siRNA-loaded nanosystems with enhanced tumor targeting and penetrating properties [56,57].

tLyP-1 (CGNKRTR) is another peptide bearing the tumor homing and CendR motif. tLyP-1-HATS nanoparticles assembled from hyaluronic acid-*g*-D-a-tocopheryl succinate (HATS) and tLyP-1-PEG-TS showed about 2-fold higher cellular uptake compared to HATS nanoparticles in CD44 and NRP-1 overexpressed MDA-MB-231, 4T1 and PC-3 cells [58,59]. DTX-loaded nanoparticles induced remarkable tumor inhibition rates of 73.5%, 79.6% and 85.1% against subcutaneous PC-3, orthotopic 4T1, and lung metastasis MDA-MB-231 tumor, respectively. Hu et al. prepared tLyP-1-functionalized PTX-loaded PEG-PLA nanoparticles that exhibited over 2-fold uptake in NRP overexpressed HUVEC and C6 cells and 2.5-fold higher anti-proliferation activity against C6 cells than unmodified nanoparticles [60]. *In vivo* studies demonstrated that PTX-loaded tLyP-1-PEG-PLA nanoparticles accumulated more and penetrated deeper in the orthotopic C6 tumor model, thus inducing increased anti-glioma efficacy with significantly prolonged survival of nude mice from 28 days (for unmodified

nanoparticles) to 38 days. Besides this, F3 and AC peptide with lengths of 35 and 15 amino acids, respectively, have been conjugated to the surface of PEG-PLA nanoparticles loaded with PTX (and PPa photosensitizer) to achieve enhancement of tumor penetration and antitumor efficacy in orthotopic glioma and subcutaneous colorectal tumor models [61–63].

After the introduction of the above mentioned tumor penetration peptides on the surface of the polymeric nanomedicines, their tumor penetration depth using diverse tumor models was usually increased. However, improvements in the ultimate therapeutic outcomes were limited. It was found that most of the polymeric nanomedicines are still based on conventional polymeric systems (such as PEG-PLA) with low circulation stability and inferior drug release behavior leading to drug leakage during circulation, low tumor accumulation and unsatisfactory intracellular drug release. It would be interesting to develop tumor penetrating peptide decorated polymeric nanomedicines integrating both high stability and fast cytosolic drug release to further enhance their anti-tumor effect. Moreover, this may be combined with other tumor penetration strategies, such as degradation of the tumor extracellular matrix and tuning of the physicochemical properties of nanomedicines by reducing their size or altering their shape.

4. Tumor cell targeting peptide for selective cellular uptake

When polymeric nanomedicines arrive at the tumor site, they first have to penetrate the extracellular matrix before they can be exposed to the cells of interest, after which they must permeate through the membrane of the cells and become localized in the desired intracellular site to release their anti-tumor contents. It should be noted that the cellular uptake of nanomedicines is usually inefficient because of the presence of a stealthy PEG coating to protect them from clearance from the circulation [64,65]. Moreover, low cell selectivity is a big hurdle for anticancer formulations. Therefore, engineering nanomedicines with active tumor cell targeting ability is of paramount importance to promote selective cellular uptake via receptor-mediated endocytosis [14,66]. After endocytosis, nanomedicines entrapped in the endosomes may release the drugs to the cytosol by osmotic swelling, membrane rupture or other mechanisms.

4.1. Integrin targeting peptide functionalized nanomedicines for tumor treatment

Cyclic RGD peptide, with a sequence of c(RGDf/yK) or c(RGDfC) and high affinity towards $\alpha_v\beta_3/\alpha_v\beta_5$ integrin that is overexpressed by angiogenic endothelial cells and most tumors, have been widely explored to furnish targeted nanomedicines through amidation or Mal-SH reaction (Table 2). For example, DOX-loaded c(RGDfK) modified PEG-*b*-poly(ε-caprolactone) (PEG-PCL) micelles showed about 3-fold higher cellular uptake in T-24 bladder cells than the non-targeted control, leading to markedly stronger cellular toxicity [67]. Pt(IV)-loaded c(RGDfK)-PEG-PLGA micelles demonstrated comparable tumor inhibition rates to free cisplatin in orthotopic MCF7MFP1 breast tumor [68]. Liu et al. reported that c(RGDfK) installation improved the antitumor efficacy of PEG-PTTMA (TTMA: 2,4,6-trimethoxybenzylidene-1,1,1-tris (hydroxymethyl) ethane methacrylate) micelles loaded with DOX in treating subcutaneous 4T1 breast tumor [69]. To further improve the

Table 2
Integrin targeting peptide modified polymeric nanomedicines used in tumor treatment studies.

Name	Sequence	Conjugate chemistry	Nanocarriers	Drug	Tumor model		Ref.
					In vitro	*In vivo*	
cRGD	c(RGDfK)	Amidation	PEG-PCL Ms	DOX	T-24, U87MG	–	[67]
			PEG-PLGA NPs	Pt(IV)	MCF-7, DU145, DU145LN2, PC3, PC3MLN4	o.t. MCF7MFP1	[68]
			PEG-PTTMA Ms	DOX	NIH 3T3, HepG2, 4T1	s.c. 4T1	[69]
			PEG-SS-PCL Ms	DOX	U87MG	s.c. U87MG	[70]
			PEG-PDTC Ms	DOX	B16	s.c. B16	[71]
			PEG-P(CL-DTC) Ms	DOX	U87MG	s.c. U87MG	[72]
			PEG-P(TMC-DTC) Ms	BP	MDA-MB-231	s.c. MDA-MB-231	[73]
			PEG-P(TMC-DTC) Ps-DM1	DM1	B16F10	s.c. B16F10	[74]
			PVA nanogels	DOX	U87MG	s.c. U87MG	[75]
	c(RGDyK)	Amidation	PEG-PTMC NPs	PTX	U87MG	s.c. & o.t. U87MG	[76–78]
			Pluronic Ms	DOX & PTX	U87MG	o.t. U87MG	[79]
			PEG-PTMBPEC Ms	DOX	B16, HUVEC	s.c. B16	[80]
			Heparin-GA NPs	GA	U87MG, HUVEC	s.c. U87MG	[81]
	c(RGDfK)XC	Mal-SH	PEG-PGlu Ms	DACHPt/ CDDP	B16F10, HUVEC, U87MG	o.t. U87MG, o.t. and LNM B16F10 & SAS-L1	[82–84]
		Aldehyde-SH	PEG-PAsp-hyd-EPI Ms	EPI	U87MG	o.t. U87MG	[85]
		Aldehyde-SH	PEG-PAsp(DET)-cholesteryl Ms	pDNA	HUVEC, HeLa	s.c. BxPC-3	[86,87]
		Aldehyde-SH	PEG-PLL(MPA)/siRNA Ms	siRNA	HeLa	s.c. HeLa	[88]
	c(RGDfC)	Mal-SH	PAMAM NPs	Pt,	PC-9, MDA-MB-231, NIH3T3	s.c. MDA-MB-231	[89]
		Mal-SH	H40-BPLP-PEG unimolecular Ms	DOX	U87MG	-	[90]
		Mal-SH	TPGS-SS-PLA NPs	PTX	A2780, A2780/T, B16F10	s.c. S180 & B16F10	[91]
		Mal-SH	PEG-P(TMC-*g*-SSDM1) prodrug	DM1	B16F10, MDA-MB-231	s.c. B16F10 & MDA-MB-231	[92–94]
		Disulfide exchange	P(PEGMA-PDSEMA) nanogels	PTX	MCF-7 & HeLa	-	[95]
RGD	GGRGD	Amidation	PEG-P(HCPT/DTDE) prodrug NPs	HCPT	HepG2 & COS7	s.c. HepG2	[96]
ATN-161	PHSCN	Amidation	PEG-P(TMC-DTC) Ps	DOX·HCl	B16F10	s.c. B16F10	[97]
cNGQ	c(CNGQGEQC)	Amidation	PEG-P(TMC-DTC) Ps	DOX·HCl	A549	o.t. & s.c. A549	[98]
		Amidation	PEG-P(TMC-DTC)-PEI Ps	siPLK1	A549	o.t. A549	[99]
OA02	c(CDGHcitGPQC)	Click chemistry	PEG-CA_8 NPs	PTX	SKOV3, ES-2, K562(-)	s.c. SKOV3	[100]

Note: Ms, micelles; Ps, polymersomes; GA, gambogic acid; XC, ε-caproic acid-cysteine; hyd, hydrazine; EPI, epirubicin; DACHPt, 1,2-diaminocylohexane platinum(II); CDDP, cisplatin, DET, diethylenetriamine.

antitumor efficacy, DOX-loaded reduction-sensitive shell-sheddable PEG-SS-PCL micelles showing reduction-triggered rapid intracellular drug release were decorated with c(RGDfK) [70]. The resulting DOX-loaded micelles exhibited 2.9-fold lower IC_{50} in U87MG cells and about 2-fold better inhibition in a subcutaneous U87MG tumor model than the non-targeted PEG-SS-PCL control. cRGD-functionalized nanomedicines have demonstrated improved antitumor activity both *in vitro* and *in vivo*. However, their inferior *in vivo* stability against dilution and protein interaction might be a major obstacle that limits effective tumor therapy. Very recently, c(RGDfK)-installed self-crosslinkable and intracellular decrosslinkable micelles loaded with DOX with superior stability, minimum drug leakage and GSH-triggered DOX release were obtained from PEG-*b*-poly(dithiolane trimethylene carbonate) (PEG-PDTC) diblock copolymer for treating B16 melanoma-bearing C57BL/6 mice [71]. These DOX containing micelles exhibited high tumor accumulation of 6.13% ID/g at 6 h post i.v. injection (3-fold higher than pegylated liposomal DOX, DOX-LPs), leading to effective tumor growth inhibition and a survival rate of 100% in an experimental period of 43 days. Moreover, c(RGDfK)-decorated disulfide-crosslinked micelles loaded with DOX based on PEG-P(CL-DTC) diblock copolymer demonstrated higher tumor inhibition efficacy in subcutaneous U87MG glioma-bearing nude mice with increasing c(RGDfK) contents (10 to 30 mol%), which were all significantly better than the tumor suppression obtained with the non-targeted control [72]. Bortezomib-pinanediol (BP)-loaded PEG-P(TMC-DTC) (TMC: trimethylene carbonate) micelles with a c(RGDfK) density of 20 mol% showed 3.6-fold more effective anticancer activity against $\alpha_v\beta_3$ overexpressing MDA-MB-231 cells than their counterparts without c(RGDfK) [73]. c(RGDfK)-directed mertansine (DM1) containing polymersomes obtained from PEG-P(TMC-DTC) via simultaneous conjugation of DM1 through the thiol-disulfide exchange reaction during fabrication exhibited a tumor inhibition rate of 93% without obvious systemic toxicity in subcutaneous B16F10 melanoma-bearing C57BL/6 mice [74]. Chen et al. reported that DOX-loaded c(RGDfK)-decorated reduction-sensitive poly(vinyl alcohol) nanogels effectively inhibited the growth of subcutaneous U87MG glioma *in vivo*, with a tumor inhibition rate of about 4.5-fold higher than the non-targeting control [75]. Moreover, several reports from different groups also demonstrated that c(RGDyK) decoration improved the tumor inhibitory effect of various polymeric nanomedicines, such as PTX-loaded PEG-PTMC nanoparticles, DOX and PTX co-loaded Pluronic micelles, DOX-loaded micelles based on PEG-*b*-poly(2,4,6-trimethoxy benzylidenepentaerythritol carbonate) (PEG-PTMBPEC), and heparin-*g*-gambogic acid prodrug nanoparticles in treating U87MG glioma and B16 melanoma models [76–81].

c(RGDfK) was further modified at the C-terminus using ε-caproic acid-cysteine, affording c(RGDfK)XC with a free thiol group that enables facile reaction with for instance Mal and aldehyde. Utilizing these strategies, Kataoka's group engineered several cRGD-functionalized PEG-polypeptide micelles for tumor-targeted delivery of cytostatic drugs [82–85], pDNA [86,87] and siRNA [88]. Platinum drug-loaded cRGD-installed PEG-*b*-poly(L-glutamic acid) (PEG-PGlu) micelles demonstrated enhanced therapeutic efficacy against both subcutaneous and orthotopic U87MG gliomas, with 5-fold lower tumor photon flux for the latter case than the controls, free oxaliplatin and drug loaded non-targeting peptide linked micelles (Fig. 2) [82]. Additionally, these micelles exhibited effective tumor growth inhibition against either primary and/or lymph node metastatic (LNM) melanoma and tongue carcinoma bearing mice [83,84]. c(RGDfK)XC modified pH-sensitive PEG-*b*-poly(aspartamide-hydrazine-epirubicin) (PEG-PAsp-hyd-EPI) prodrug micelles showed 4-fold enhanced accumulation in orthotopic U87MG glioma than their non-targeted control, resulting in 12-fold better tumor suppression [85]. After surface modification with c(RGDfK)XC, siRNA-loaded disulfide-crosslinked micelles based on PEG-*b*-poly(L-lysine) diblock copolymer modified with 1-(3-mercaptopropyl)amidine (PEG-PLL(MPA)) also significantly promoted tumor accumulation and gene silencing in a subcutaneous HeLa-Luc cervical cancer model [88].

cRGD with a sequence of c(RGDfC) was introduced onto various polymeric nanosystems mainly through Mal-SH Michael addition for targeted delivery of photothermal agents or cytostatic agents to treat subcutaneous tumors including triple-negative breast tumor, sarcoma and melanoma. Zhou et al. reported c(RGDfC) decorated dendrimer encapsulating platinum nanoparticles (DEPt) for targeted photothermal therapy of subcutaneous MDA-MB-231 breast tumor-bearing BALB/c nude mice [89]. cRGD-DEPt delivered much higher Pt content into the tumor site at 12 and 24 h post injection than the DEPt group, thus leading to faster temperature increase upon NIR irradiation to a final temperature of 45.4 °C at 24 h and significantly suppressed tumor growth. c(RGDfC) modified unimolecular micelles based on H40-biodegradable photo-luminescent polymer (BPLP)-PEG hyperbranched polymer (H40-BPLP-PEG-cRGD) improved DOX delivery to U87MG cells, leading to higher cytotoxicity than H40-BPLP-PEG micelles [90]. Guo et al. conjugated c(RGDfC) to the surface of PTX-loaded Mal-functionalized reduction-sensitive D-α-tocopherol polyethylene glycol succinate-SS-poly(lactide) (TPGS-SS-PLA) nanoparticles [91]. The resulting targeting nanoparticles revealed significantly enhanced PTX accumulation and toxicity in B16F10, A2780 and PTX-resistant A2780/T cells and about 2-fold better tumor inhibition in subcutaneous S180 sarcoma and B16F10 melanoma-bearing Kunming mice than the non-targeted control and Taxol®. Our group recently developed c(RGDfC)-functionalized reduction-sensitive micellar DM1 prodrug (cRGD-MP-DM1) from PEG-P(TMC-g-SSDM1) that showed over 2-fold better inhibition of B16F10 and MDA-MB-231 cells than non-targeted MP-DM1 [92,93]. *In vivo* studies demonstrated that cRGD-MP-DM1 improved the maximum tolerated dose of DM1 by 3-fold and these micelles were potent in suppressing the growth of subcutaneous B16F10 and MDA-

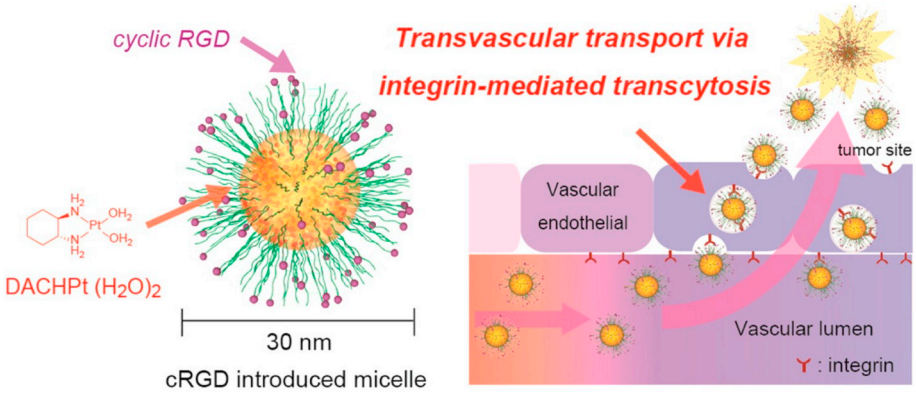


Fig. 2. cRGD-linked polymeric micelles for integrin-mediated transcytosis and targeted delivery of platinum drugs to glioblastoma. Reproduced with permission from ref [82].

MB-231 tumors, with tumor inhibition rates of 97.5% and 87.6%, respectively. cRGD-MP-DM1 were further loaded with DTX, achieving targeted synergistic treatment of subcutaneous B16F10 melanoma and nearly complete tumor elimination with a lower DM1 dosage [94]. Adopting the thiol-disulfide exchange procedure, c(RGDfC) decorated nanogels were obtained from poly(polyethylene glycol monomethyl ether methacrylate-*co*-pyridyl disulfide ethyl methacrylate) (P(PEGMA-PDSEMA)) polymer, which selectively transported PTX to HeLa cells [95].

Linear RGD, GGRGD, was introduced onto the surface of reduction-sensitive prodrug nanoparticles based on PEG-*b*-poly(dithiodiethanol-alt-10-hydroxycamptothecin) (PEG-P(HCPT/DTDE)) [96]. As a result of the RGD incorporation, these prodrug nanoparticles induced about 4-fold enhanced cellular uptake in HepG2 cells and over 2-fold accumulation in a subcutaneous HepG2 hepatoma xenograft, thus efficiently suppressing the tumor growth resulting in 4-fold lower tumor volume than that obtained with the PBS treated group.

In addition to RGD, ATN-161, cNGQ and OA02 peptide targeting to $\alpha_5\beta_1$, $\alpha_3\beta_1$ and α_3 integrin, respectively, have also been used to modify polymeric nanosystems for improved delivery of cytostatic drugs and siRNA to tumors. Our group recently reported that ATN-161 and cNGQ peptide functionalized disulfide-crosslinked PEG-P(TMC-DTC) polymersomes could efficiently load and deliver DOX·HCl to lung tumor and melanoma bearing nude mice, respectively [97,98]. Moreover, cNGQ-decorated chimeric PEG-P(TMC-DTC)-PEI polymersomes (cNGQ-RCCP) were employed for high-efficiency targeted delivery of Polo-like kinase1 specific siRNA (siPLK1) to orthotopic A549 lung cancer bearing nude mice (Fig. 3) [99]. The *in vitro* and *in vivo* studies showed that siPLK1-cNGQ-RCCP substantially down regulated the PLK1 mRNA level in A549-luc cells and effectively inhibited tumor growth. OA02 peptide was demonstrated to enhance the cellular uptake of PEG-*b*-dendritic cholic acids (PEG-CA_8) nanoparticles in α_3-positive SKOV3 and ES-2 ovarian cancer cells [116]. After loading PTX, OA02-PEG-CA_8 nanoparticles exhibited superior antitumor efficacy against SKOV3 tumor cells in vitro and in vivo than the non-targeted particles.

These integrin targeting peptide-decorated polymeric nanomedicines are promising in treating various malignancies, such as melanoma, triple-negative breast tumor, lung and glioma. Moreover, disulfide-crosslinking strategy can be integrated to afford superb *in vivo* stability of the nanosystems with fast intracellular drug release, increasing the drug accumulation in the tumor site and drug concentration inside cancer cells to improve tumor therapy. It is interesting to note that optimized integrin targeting, in particular cRGD-modified nanosystems can further be incorporated with drug combinations to overcome drug resistance and ablate cancer stem cells.

4.2. EGFR targeting peptide functionalized nanomedicines for tumor treatment

GE11 peptide with a main sequence of YHWYGYTPQNVI was reported to have high affinity towards epidermal growth factor receptor (EGFR) that is overexpressed in a variety of tumors [101]. Hence, it has been conjugated to a series of polymeric nanoparticles for tumor targeted delivery of anticancer drugs [102–106] and photosensitizers [107,108] (Table 3). For instance, Milane et al. demonstrated that GE11-functionalized PEG-PLGA/PCL blend nanoparticles had enhanced

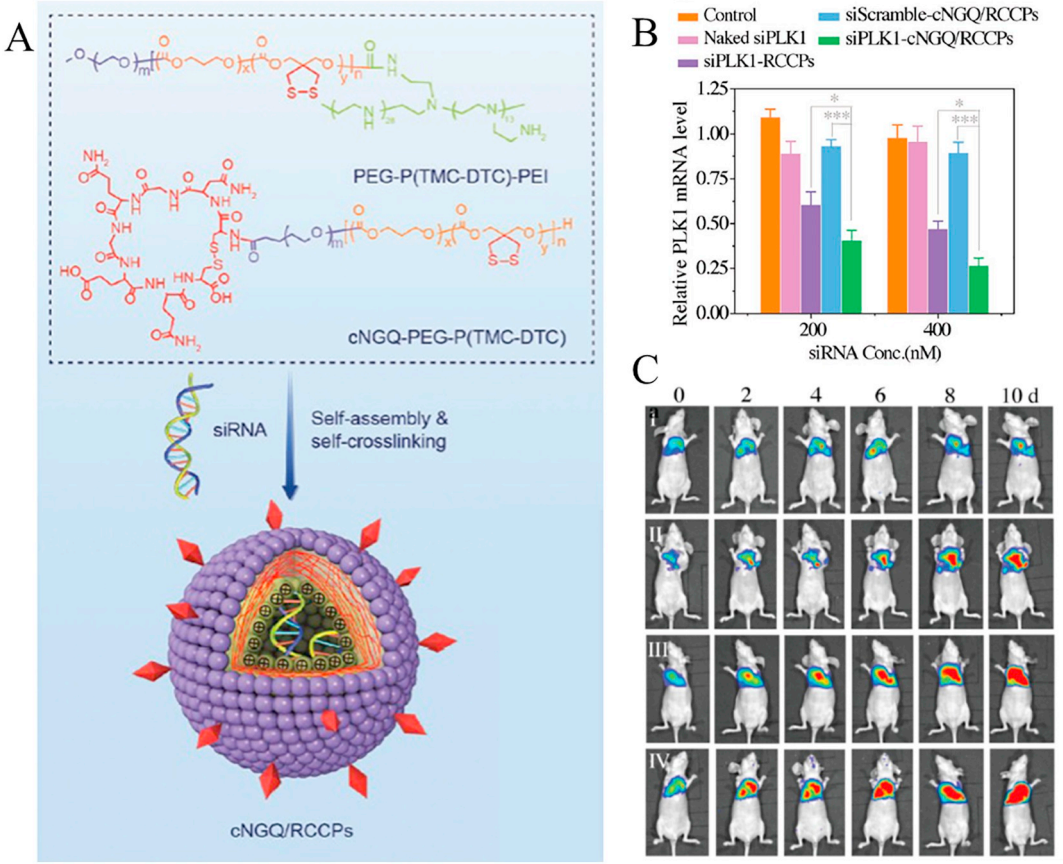


Fig. 3. cNGQ–decorated chimeric PEG-P(TMC-DTC)-PEI polymersomes (cNGQ/RCCPs) for targeted delivery of siRNA to orthotopic lung cancer bearing nude mice. (A) Scheme showing the formation of siRNA–loaded cNGQ/RCCPs. (B) Gene-silencing ability of siPLK1-cNGQ/RCCPs in A549-luc cells following 48 h incubation (n = 4). (C) Luminescence optical images of nude mice bearing orthotopic A549-luc tumors following treatment with siPLK1-cNGQ/RCCPs (I), siPLK1-RCCPs (II), siScramble-cNGQ/RCCPs (III), and PBS (IV), respectively. The mice were intravenously injected with a dosage of 2 mg siRNA equiv. kg^{-1} on day 0, 2, 4, 6 and 8. Reproduced with permission from ref [99].

uptake in SKOV3 and MDA-MB-231 cells at 15 min and in OVCAR5 cells up to 1 h incubation compared to non-targeted nanoparticles [102]. These EGFR-targeted nanoparticles, after co-loading lonidamine (LND) and PTX, were potent in inhibiting the growth of drug sensitive and drug resistant cells. Aminoflavone (AF)-loaded PAMAM-PLA-PEG-GE11 unimolecular micelles significantly suppressed the growth of orthotopic MDA-MB-468 triple negative breast tumor, with over 10-fold lower tumor volume relative to the non-targeted control [103]. GE11-linked prodrug micelles based on PEG-*b*-poly(2-methyl-2-carboxyl-propylene carbonate)-*g*-gemcitabine/dodecanol (PEG-*b*-PCC-*g*-GEM/DC) showed improved cellular uptake and cytotoxicity in MIA PaCa-2 cells as well as significantly enhanced antitumor efficacy in an orthotopic pancreatic tumor compared to non-targeted controls [104]. Very recently, our group decorated doxorubicin hydrochloride (DOX·HCl)-loaded PEG-P (TMC-DTC) polymersomes with GE11 that significantly prolonged the survival rate of orthotopic SMMC-7721 hepatoma-bearing Balb/c mice with median survival time of 130 days versus 70 days for non-targeted polymersomes [105]. In addition, these DOX·HCl-loaded EGFR-targeted polymersomes also showed efficient suppression of subcutaneous SKOV3 ovarian tumor with a 100% survival rate in an experimental period of 78 days, outperforming clinically used DOX-LPs with steady tumor growth and body weight loss [106]. Master et al. utilized GE11-modified PEG-PCL micelles to load the photosensitizer silicon phthalocyanine-4 (Pc 4), which demonstrated obvious cell killing upon light irradiation in both A431 and SCC-15 carcinoma cells [107,108]. *In vivo* studies indicated that EGFR-targeted micellar Pc 4 had better tumor inhibition with a tumor volume of over 4-fold lower than the non-targeted control.

Apart from chemotherapy and photodynamic therapy, GE11-tethered nanosystems are also appealing in delivering biotherapeutics including siRNA [109–111], DNA [112–114] and protein drugs [115] to treat lung, hepatoma, breast and ovarian tumors. Nascimento et al. utilized GE11-decorated chitosan-PEG (CS-PEG-GE11) nanoparticles for targeted delivery of siMad2, a siRNA, silencing the essential mitotic checkpoint gene Mad2, to EGFR overexpressed cisplatin sensitive and resistant (DDP®) A549 cells [110,111]. This system efficiently inhibited the expression of Mad2 in tumor cells and further combination treatment with cisplatin induced significantly more effective tumor inhibition against both A549 and A549-DDP® xenografts than the non-targeted control. Bioreducible branched polyethylenimine based GE11-conjugated PEG-bPEISS polymers efficiently complexed with pDNA and showed higher accumulation in subcutaneous A549 lung tumor than non-targeted polyplexes [112]. Interestingly, the tumor targeting ability of PEG-bPEISS polyplexes was further improved by introducing branched GE11 peptide, likely due to its multivalent interaction with EGFR. Klutz et al. reported that GE11-PEG-PEI complexed with sodium iodide symporter complementary DNA (NIS-cDNA) caused a 22-fold increased iodide uptake in Huh-7 cells and that the iodide uptake is directly correlated with the EGFR expression levels on different cancer cell lines [113]. After three or four administrations of GE11-polyplexes/^{131}I, the tumor growth of subcutaneous Huh-7 hepatoma was significantly delayed, thus prolonging the survival of mice. To achieve EGFR and CD44 dual-targeted delivery of granzyme B (GrB) protein drugs, our group developed GE11-modified hyaluronic (GE11-HA) nanogels [115]. GE11-HA nanogels showed more than 6-fold higher uptake in EGFR and CD44-positive SKOV3 cells than HA nanogels. Accordingly, GrB-loaded GE11-HA nanogels induced stronger growth inhibition of SKOV3 cells *in vitro* and almost complete tumor growth suppression of subcutaneous SKOV3 ovarian carcinoma and MDA-MB-231 breast tumor *in vivo*, which was much more effective than GrB-loaded HA nanogels.

4.3. Other targeting peptides for functionalization of nanomedicines to be used for tumor treatment

Aside from integrin and EGFR targeting peptides, a variety of peptides targeting other receptors that are overexpressed in different tumor types, blood vascular endothelium, or some specific tumors have been used to modify various polymeric nanomedicines to mediate targeted cancer therapy (Table 4). CC9-functionalized RCCP loaded with pemetrexed disodium (PEM) exhibited a 22-fold longer circulation time and 9.1-fold higher accumulation in subcutaneous H460 tumor than the clinically used Alimta®, leading to about 3 and 5-fold more effective tumor suppression than non-targeting PEM-RCCP and Alimta®, respectively [116]. MC11 peptide targeting fibroblast growth factor receptor (FGFR) and LHRH peptide targeting luteinizing hormone-releasing hormone receptor (LHRHR) have also been used for targeted delivery of plasmid DNA and DOX to ovarian tumor bearing mice, respectively [117,118]. Urokinase plasminogen activator receptor (uPAR) targeted PEG-PLGA nanoparticles were engineered via conjugating uPA peptide for co-delivery of anti-miR-21 and anti-miR-10b to triple negative MDA-MB-231 breast tumor bearing nude mice [119]. The targeted co-delivery systems resulted in 40% more tumor reduction than their non-targeted counterparts. Yu et al. found that IF7 peptide on the surface of PTX-loaded PEG-PLA nanoparticles endorsed specific targeting of tumor vasculature via IF7-annexin 1 interaction, thus resulting in higher accumulation in the tumor site and significant antitumor efficacy towards drug resistant MCF-7 breast tumor [120]. Moreover, the D-peptide form of IF7 (RIF7) has been introduced to layered reducible HA/PAMAM$_{SS}$/pDNA nanoparticles for dual-targeted therapeutic gene delivery to subcutaneous A549 and U87MG tumor as well as pulmonary metastatic melanoma [121]. Meanwhile, Coop,

Table 3
GE11 peptide modified polymeric nanomedicines used in tumor treatment studies.

Sequence	Conjugate chemistry	Nanocarriers	Drug	Tumor model		Ref.
				In vitro	*In vivo*	
YHWYGYTPQNVIGGGGC	Mal-SH	PEG-PLGA/PCL NPs	PTX & LND	SKOV3, OVCAR5, MDA-MB-231	–	[102]
	Mal-SH	PAMAM-PLA-PEG unimolecular Ms	AF	MDA-MB-468	o.t. MDA-MB-468	[103]
	Mal-SH	PEG-P(CC-GEM/DC) Ms	GEM	MIA Paca-2	o.t. MIA Paca-2	[104]
	Mal-SH	H40-P(Asp-AED-ICA)-PEG unimolecular NPs	GFP-siRNA	MDA-MB-468	–	[109]
	Mal-SH	CS-PEG NPs	siMad2	A549, A549-DDP®	s.c. A549, A549-DDP®	[110,111]
	Mal-SH	PEG-bPEI-SS/DNA polyplexes	pDNA	A549, Huh-7	s.c. A549	[112]
CYHWYGYTPQNVI	disulfide exchange	PEG-PEI/DNA polyplexes	NIS-cDNA	Huh-7, SKOV3	s.c. Huh-7	[113]
	Mal-SH	PEG-PCL NPs	Pc-4	A431, SCC-15, MCF-7	s.c. SCC-15	[107,108]
YHWYGYTPQNVI	amidation	PEG-P(TMC-DTC) Ps	DOX·HCl	SMMC-7721, K562, SKOV3	o.t. SMMC-7721, s.c. SKOV3	[105,106]
	amidation	HA nanogels	GrB/CC	SKOV3	s.c. SKOV3, MDA-MB-231	[115]

Note: Ms, micelles

Table 4
Targeting peptide modified polymeric nanomedicines used for tumor treatment.

Peptide	Sequence	Target	Conjugate chemistry	Nanocarriers	Drug	Tumor model		Ref.
						In vitro	*In vivo*	
CC_9	CSNIDARAC	–	Amidation	PEG-P(TMC-DTC)-PEI Ps	PEM	H460	s.c. H460	[116]
MC11	MQLPLATGGGC	FGFR	Disulfide exchange	PEI-β-CD/Ad-SS-PEG	pDNA	SKOV3, PC-3, HepG2, HeLa,	s.c. SKOV3	[117]
LHRH	EHWSYGLRPG	LHRHR	Aldehyde-NH_2	HA-cys-ADOX NPs	DOX	NIH3T3, OVCAR-3	o.t. OVCAR-3	[118]
uPA	VSNKYFSNIHWGC	uPAR	Amidation	PEG-PLGA NPs	anti-miR-21 & anti-miR-10b	MDA-MB-231	s.c. MDA-MB-231	[119]
IF7	IFLLWQR	Annexin 1	Aldehyde-NH_2	PEG-PLA NPs	PTX	HUVEC	s.c. MCF/ADR	[120]
RIF7	RQWLLFI	Annexin 1	Amidation	HA/PAMAM/pDNA	pDNA-shCyclin	HUVEC, U87MG, B16F10	s.c. A549 & U87MG metastatic B16F10	[121]
CooP	ACGLSGLGVA	MDGF	Mal-SH	PEG-PLA NPs	PTX	HUVEC, U87MG	o.t. U87MG	[122]
CGKRK	CGKRK	Heparan sulfate	Mal-SH	PEG-PCL NPs	PTX	U87MG, HUVEC	s.c. U87MG	[123]
PNP	c(CMPRLRGC)	LDLR	Amidation	PEG-PLA NPs	PTX	C6, BCECs, H9c2(2-1)	o.t. C6	[124]
CK	CVNHPAFACGYGHTMYYHHYQHHL	SHH & VEGF-2	Amidation	PEG-PLA NPs	PTX	HUVEC, U87MG	o.t. U87MG	[125]
RVG	YTIWMPENPRPGTPCDIFTNSRGKRASNG	nAChR	Amidation	PLGA NPs	siMyc, siBcl-2, siVEGF	Neuro 2A	s.c. Neuro 2A	[126]
PTP	KTLLPTP	Plectin-1	Click chemistry	bPEG-SS-PAMAM NPs	siTR3 & PTX	Panc-1	s.c. Panc-1	[127]
T7	CHAIYPRH	Transferrin receptor	Mal-SH	PEG-PAMAM	pORF-TRAIL & DOX	Bel-7402	s.c. Bel-7402	[128]
SP94	SFSIILTPILPLGGC	–	Disulfide exchange	Ad-PEG-SP94, Ad-SS-PEG, PEI-hbCD NPs	miR-34a	LM3, HL-7702	s.c. LM3	[129]
LP_7	LPLTPLP	Hsp90	Amidation	PLGA NPs	DTX	A549, H1975	s.c. A549	[130]
AHP	FCDGFYACYKDV	Her2	Amidation	AHP-HA-HAD/PLGA NPs	SN38	HGC27	s.c. HGC27	[131]

Note: Ps, polymersomes; NPs, nanoparticles

Table 5
Cell penetration peptide modified polymeric nanomedicines used for tumor treatment.

Peptide	Sequence	Conjugate chemistry	Nanocarriers	Drug	Tumor model		Ref.
					In vitro	*In vivo*	
Penetratin	RQIKIWFQNRRMKWKKGG	Amidation	CS-Lin-Pen Ms	pDNA	HEK 293, CHO, HeLa	–	[136]
	RQIKIWFQNRRMKWKKGGC	Mal-SH	Pen/FA-PEG-DSPE/PLGA NPs	siRNA, anti-miR-155	KB, Pre-B, Toledo B	s.c. KB & pre-B	[137] [138]
R8	RRRRRRRRC	Disulfide exchange	R8-PEI-β-CD/pDNA polyplexes	pDNA	A549, C6	s.c. C6	[139]
LNP	KKRTLRKNDRKKRC	Mal-SH	DGL-PEG-LNP NPs	pcDNA3.1-ING4	U87, BCEC, Bel-7402, SH-SY5Y	o.t. U87	[140]
TAT	RKKRRQRRR	Amidation	CS-*g*-TAT NPs	siRNA^{Sur}	4T1, MCF-7	o.t. 4T1	[141]
	GCGGGYGRKKRRQRRR	Mal-SH	PLA-PHis-PEG/PHis-PEG Ms	DOX	MCF-7, A549, HL-60, HL-60/MX2, NCI/ADR-RES	s.c. A549, MCF-7 & A2780/AD	[142]
	CYGRKKRRQRRR	Mal-SH	TAT-PEG-PE, PEG-pp-DOX, miRNA-SS-PE Ms	DOX, miRNA-34a	HT1080, MCF-7	–	[143]
	YGRKKRRQRRRC	Mal-SH	TAT-PEG-PHEP NPs	DOX, IR-780	MDA-MB-231, Raw 264.7	o.t. MDA-MB-231	[144]
		Mal-SH	PAEP(Cys/DTPA)-PCL, TAT-PEG-PCL NPs	Ce6, Gd^{3+}	BxPC-3	s.c. BxPC-3	[145]
		Mal-SH	TAT-PEG-PCL Ms	DOX	SKOV3, Bcap-37, MCF-7/DOX®	s.c. Bcap-37	[146]
ppTAT	GPLGIAGQYGRKKRRQRRRC	Amidation	PEG-ppTAT-DOX prodrug NPs	DOX	A549, MCF-7, HT1080, NCI/ADR-RES	–	[147]
PF14	AGYLLGHLLOOLAAAALOOLL	Amidation	PEG-pp-PF14/DNA complexes	pDNA	CHO, U87MG, Neuro2a	s.c. Neuro2a	[148]
UPA-R9	EEEEEEEEC6GSGRSAGRRRRRRRRRC6C	Mal-SH	PEG-PLA NPs	PTX	C6	o.t. C6	[149]
R9	RRRRRRRRR	Amidation	PEG-D*link*$_m$-R9-PCL NPs	siCDK4	A549	s.c. A549	[150]
R8NLS	CRRRRRRRRVKRKKKP	Mal-SH	PHPMA-*g*-H1/R8NLS-DA conjugates	H1 peptide	HeLa	s.c. HeLa	[151]
			PHPMA-*g*-DOX-R8NLS, P(HPMA-APMA-DA) NPs	DOX	HeLa	s.c. HeLa	[152]

Note: Ms, micelles; NPs, nanoparticles

CGKRK, PNP and CK peptides that target mammary-derived growth factor (MDGF), heparan sulfate, low-density lipoprotein receptor (LDLR) and both human sonic hedgehog (SHH) and VEGFR-2 receptors, respectively, have been conjugated to PTX loaded PEG-PLA or PEG-PCL nanoparticles to achieve simultaneous targeting of tumor angiogenic blood vessels and tumor cells in orthotopic or subcutaneous glioma bearing mice, leading to more accumulation in the tumor and much longer survival times [122–125]. RVG peptide, targeting nicotinic acetylcholine receptor (nAChR) expressed in neural cells, was conjugated to the surface of PLGA nanoparticles for specific targeted delivery of a gene cocktail of siMyc, siBcl-2, and siVEGF and effective treatment of Neuro 2A neuroblastoma [126]. PTP peptide was coupled to the redox sensitive branched PEG-G2 dendrimer (bPEG-SS-PAMAM) for targeted co-delivery of PTX and siTR3, therefore synergistically inhibiting the tumor growth and inducing cell apoptosis of Panc-1 pancreatic tumor [127]. T7 peptide modified PEG-PAMAM was complexed with pORF-hTRAIL-DOX to achieve targeted combination therapy, which more efficiently inhibited tumor growth *in vitro* and *in vivo* than single therapy against transferrin receptor overexpressing Bel-7402 hepatoma [128]. SP94 peptide was conjugated to the surface of redox responsive PEG-PEI supramolecular complexes for targeted delivery of tumor suppressor miR-34a to LM3 hepatoma [129]. The resulting complexes significantly increased the miR-34a expression level in the xenograft tumor, which was 500-fold higher than that of the PBS treated group and hence effectively inhibiting the tumor growth with tumor sizes of around 9 or 30-fold lower than those obtained with the non-targeted control and PBS group, respectively. Zuo and coauthors screened a dual functional peptide LPLTPLP that can target non-small cell lung cancer specimens and inhibit the expression of heat shock protein 90 (Hsp90), one of the mostly studied anticancer targets [130]. LPLTPLP modified DTX-loaded PLGA nanoparticles induced higher antitumor efficacy against A549 tumor cells both *in vitro* and *in vivo* with around 2-fold lower IC_{50} and tumor weight than non-targeted nanoparticles. Yang et al. reported AHP peptide modified HA/PLGA nanoparticles for Her2 and CD44 dual targeted delivery of 7-ethyl-10-hydroxy-camptothecin (SN38) [131]. These dual-targeting nanoparticles exhibited enhanced tumor accumulation and significantly higher tumor growth inhibition in HGC27 gastric tumor bearing Balb/c nude mice than clinically used irinotecan and other nanoparticle formulations.

These peptide-modified targeted polymeric nanomedicines are mostly constructed from FDA approved or well-recognized biocompatible and biodegradable polymers (e.g. PEG, polyesters, polycarbonates, polypeptides), which can effectively reduce safety issues. Moreover, some systems are integrated with disulfide-crosslinking strategies and modulated to a small size to afford superb in vivo stability, enhanced tumor penetration and fast intracellular drug release, overcoming the main delivery barriers to improve tumor therapy. Nevertheless, estimations of the percentage and mechanisms involved in the escape of targeted nanomedicines from the endo/lysosomal compartments remain unclear and are frequently neglected by the investigators. It's desirable to further develop endosomal escape strategies and incorporate these in the optimization of targeted nanosystems for complete elimination of tumor cells.

5. Cell penetration peptides for intracellular delivery

Targeting peptides, although inducing enhanced cellular uptake and antitumor efficacy of polymeric nanomedicines to different types of tumor-bearing mice, remain with limitations to achieve successful clinical translation. This is most likely due to their receptor dependent behavior and the different receptor expressions on the cell surface originating from tumor heterogeneity [132,133]. An alternative approach to promote tumor cell uptake of polymeric nanomedicines was recently developed using cell penetration peptides (CPP), which are usually cationic peptides rich in arginine and lysine units and which

facilitate penetration of cells independent from the receptors via electrostatic interaction with the negatively charged cell membranes [32,134,135].

CPP-decorated polymeric nanoparticles have been engineered to facilitate intracellular delivery of proteins, enzymes, and genes (Table 5) [136–141]. For example, Layek et al. found that penetratin functionalized chitosan-*g*-linoleic acid (CS-Lin) micelles were highly efficient in transporting pDNA into diverse cells, with 30-40 fold higher gene transfection than the CS-Lin system [136]. Penetratin-modified siRNA or anti-miR-155-loaded PLGA nanoparticles could silence the luciferase gene or significantly suppress the tumor growth *in vivo*, respectively, by intra-tumor injection [137,138]. Gao and coauthors demonstrated that CS-*g*-TAT could assist therapeutic $siRNA^{Sur}$ targeting survivin to reduce the proliferation, tumor growth and metastasis of 4T1 breast tumor by intra-tumor injection [141]. It should be noted, however, that these systems although with good *in vitro* performance, may be associated with fast clearance and wide distribution in most organs after *i.v.* administration due to the inherent cationic nature and non-selectivity of CPPs. This may cause severe systemic toxicity and low antitumor efficiency. Therefore, activatable CPP systems that shield CPPs during circulation while becoming activated in the tumor site have received tremendous attention in the past decade.

Activatable CPP systems are generally constructed by physical or chemical protection of CPP to shield its positive charge in the circulation, while de-shielding has to take place in the extracellular environment to overcome the barriers of fast clearance and low cellular uptake simultaneously. PEG shielding has been the most popular physical protection strategy for CPPs. Bae's group prepared activatable TAT-functionalized micelles by co-assembly of $PEG_{3.4k}$-*b*-poly(L-histidine)$_{5k}$ (PEG-PHis) and TAT-$PHis_{2k}$-PEG_{2k}-PLA_{3k}, wherein, TAT was protected by PEG at pH 7.4 while it became exposed in the slightly acidic tumor extracellular environment due to the ionization of the PHis block [142]. These DOX-loaded micelles significantly regressed various xenograft tumors in BALB/c nude mice including subcutaneous MCF-7 breast tumor, A549 lung tumor, KB epidermoid tumor, and drug resistant A2780/AD ovarian tumor. Based on the upregulated expression of MMP-2 in many types of tumors, Salzano et al. reported MMP-2 responsive shell detachable TAT-functionalized mixed polymeric micelles constituting of MMP-2 sensitive PEG_{2k}-pp-DOX, reduction-sensitive miRNA-34a-SS-PE (pp: GPLGIAGQ, PE: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine), TAT-PEG_{1k}-PE and PEG_{1k}-PE for targeted co-delivery of DOX and miRNA-34a to MMP-2 overexpressing cancer cells [143].

Apart from the physical PEG shield, some chemical approaches were also explored to shield the CPP during circulation, while fully recovering its function in the specific tumor extracellular environment (acidic pH, MMP-2 etc.). Li et al. employed 2,3-dimethylmaleic anhydride (DA) to mask TAT on the surface of PEG-*b*-poly(2-hexoxy-2-oxo-1,3,2-dioxaphospholane) (PEG-PHEP) nanoparticles for the co-delivery of IR780 and DOX (^{DA}TAT-$NP_{IR\&DOX}$) [144]. The resulting nanoparticles were inert for RES clearance during circulation, while they became reactivated upon arriving at the tumor site with a slightly acidic pH to promote its cellular internalization. Subsequently, these nanoparticles quickly released DOX to the cell nucleus under NIR irradiation and effectively inhibited the growth of MDA-MB-231 breast tumor. Similarly, chlorin e6 (Ce6) and Gd^{3+} co-loaded ^{DA}TAT-NP based on ^{DA}TAT-PEG-PCL and PAEP(Cys/DTPA)-PCL were used for fluorescence and magnetic resonance imaging guided photodynamic therapy of BxPc-3 pancreatic tumor bearing BALB/c nude mice [145]. Jin et al. amidized the lysine residual amines of TAT with succinyl chloride (^{a}TAT) to inhibit the non-specific interaction of TAT in the blood [146]. Reactivation took place in the acidic tumor interstitium and intracellular endo/lysosomes. ^{a}TAT-tethered PEG-PCL micelles had a similar circulation profile as PEG-PCL micelles, which was much longer than that of TAT-modified micelles. Moreover, ^{a}TAT-PEG-PCL micelles much more efficiently accumulated and delivered DOX to tumor tissues, leading to higher antitumor activity against subcutaneous Bcap-37 breast tumor. Tu et al. reported that MMP-2-sensitive PEG-ppTAT-DOX prodrug nanoparticles could inhibit the non-specific interaction of TAT via PEGylation while promoting the cellular uptake of nanoparticles by MMP-2 mediated shedding of the PEG shell and exposure of TAT [147]. These prodrug nanoparticles exhibited MMP-2 dependent cellular uptake, P-gp inhibiting ability and high antitumor activity to both drug sensitive and resistant cancer cell lines. MMP-2-sensitive PEG-pp-PF14/DNA complexes exhibited specific induction of gene expression in a subcutaneous Neuro2a tumor [148]. With a similar strategy, activatable nona-arginine (R9) sensitive to tumor overexpressing urokinase plasminogen activator was employed to guide PTX-loaded PEG-PLA nanoparticles targeting to orthotopic glioma bearing nude mice with prolonged survival time [149]. Sun et al. developed a pH-sensitive linker bridged PEG-Dm-R9-PCL copolymer for targeted delivery of siRNA to A549 lung tumor [150]. PEG-Dm-R9-PCL micelles were able to shed PEG and expose R9 at pH 6.5, thus improving the transportation and silencing efficiency of siCDK4 *in vitro* and *in vivo*, resulting in pronounced tumor growth inhibition. DA masked R8NLS peptide with both nuclear targeting and cell penetration capability, was employed for targeted delivery of DOX or therapeutic H1 peptide based on multistage stimuli sensitive PHPMA polymeric nanosystems to subcutaneous HeLa tumor-bearing nude mice. The nuclear drug accumulation was enhanced by up to 50 fold compared with their non-targeted counterparts, resulting in efficient tumor growth inhibition [151,152].

The major advantage of CPPs lies in their capability to transport nanomedicines into the cells by direct transduction exempting the endosomal entrapment. Considering the lack of cell specificity of CPPs, CPP-decorated nanomedicines should be designed with an inert surface using physical or chemical shielding to avoid fast clearance and non-specific interactions during the circulation. After vascular extravasation and accumulation at the tumor site, CPP should be exposed via de-shielding using the unique extracellular environment with slightly acidic pH and evaluated levels of MMP-2 to boost the intracellular delivery of nanomedicines and their cargos. In this case, the complex extracellular environment and tumor heterogeneity also need to be considered carefully. Moreover, it would be desirable to develop CPP-modified nanomedicines, which can be exposed by switching between an inert and an active state while maintaining a simple design and easy fabrication.

6. Endosomal disrupting peptide for cytosolic delivery

Successful cytosolic delivery of therapeutic agents, in particular proteins, siRNA and DNA, is important for exerting the intended function of tumor-related polymeric delivery systems. It should be noted that polymeric nanoparticles mainly enter cells via the endocytic pathway and are entrapped in endo/lysosomes, in which biotherapeutics are at risk for degradation by active enzymes as well as the acidic pH [153,154]. This results in limited delivery of therapeutic agents to the intracellular targets and thus inferior antitumor efficacy. To this end, several peptides with endosomal escape capability have been utilized to aid nanomedicines escaping from endo/lysosomal degradation and presenting better cancer therapy.

Melittin, a cationic and non-specific membrane lytic peptide with amphipathic α-helical structures in aqueous solution, was conjugated to P(OEGMA-DMA)-P(DPA-PDSEMA) diblock copolymer through the thiol-disulfide exchange reaction [155]. These polymers self-assemble into micelles at physiological pH with melittin buried within the hydrophobic core and are disassembled at acidic pH (pH 5.7), unveiling the melittin peptide and enhancing hemolytic activity. *In vitro* studies demonstrated that melittin-functionalized polymers significantly improve endosomal release of DNA, transfecting 13 to 60-fold more cells (HeLa, KB, A549 and Z310) than control polymers without peptide. Moreover, melittin-functionalized polyplexes containing luciferase pDNA showed 82.5 and 59.7-fold higher luciferase activity in KB and

A549 tumor, respectively, compared to control polyplexes. Golan et al. conjugated a subunit of the influenza virus hemagglutinin (HA2) with the ability to disrupt endosomal membranes, to PHPMA-R8 copolymer for promoting endosomal escape of RAC1 siRNA, which effectively induced RAC1 silencing and inhibited the target gene expression for more than 40% [156]. Histidine peptide with buffering capacity and proton sponge effect has also been introduced to chitosan based gene delivery systems, leading to rapid endosomal escape, effective cytosolic siRNA release and efficient inhibition of tumor growth and metastasis [157].

Though endosomal escape is a critical step in the application of polymeric nanomedicines for anti-cancer therapy, up to now the strategies which have been applied to boost cytosolic delivery are very limited. Proton-sponge effect, pore formation, membrane fusion and photochemical membrane disruption represent the mostly proposed mechanisms for endosomal membrane destabilization [153]. For polymeric nanomedicines, in particular polyplexes, that contain high buffering capacity polymers (e.g. PEI, PLL, PAMAM) with extensive translocation of ions will lead to endosomal membrane rupture. This represents an easy and direct way to facilitate endosomal escape without extra modification. Regarding the peptide-modified systems, the use of fusogenic peptides will induce endosomal escape in a natural manner (fusion) and this strategy will result in a safe release of therapeutics. In addition, engineering polymeric nanomedicines that will be taken up by a non-endocytic pathway would also be an intriguing alternative.

7. Blood brain barrier penetrating peptide for functionalization of nanomedicines to be used for glioma treatment

Glioblastoma is a lethal brain tumor with poor prognosis and represents one of the most aggressive human malignancies. Effective glioma treatment strategies remain to be explored mainly due to the presence of the BBB, which hinders the translocation of chemotherapeutics towards the tumor site [158,159]. It has been reported that receptor-mediated transcytosis is one of the mechanisms to enhance BBB penetration and various receptors overexpressed on the brain capillary endothelial cells (BCECs, important component of BBB) have shown potential in aiding therapeutics to cross the BBB [34,35]. Notably, low-density lipoprotein receptor-related protein-1 (LRP1) is overexpressed not only in BCECs but also in glioma cells. As a ligand to LRP1, angiopep-2 (ANG) peptide with a sequence of TFFYGGSRGKRNNFKTEEY has demonstrated superb BBB crossing capability in transporting cytostatic drugs, wherein, two ANG–drug conjugates are in clinical trials [160,161]. Moreover, ANG has been utilized to transport a variety of polymeric nanomedicines into glioma. For instance, as a result of ANG decoration, PTX-loaded PEG-PCL nanoparticles exhibited a 3.8-fold higher inhibitory effect to U87MG cells and 1.7-fold higher transport ratio across the BBB in an *in vitro* model using BCECs monolayer [162]. Consequently, 1.8-fold enhanced anti-glioma effect and significantly prolonged survival was observed in orthotopic U87MG glioma-bearing nude mice [163]. Luo et al. prepared ANG-modified high-intensity focused ultrasound (HIFU) responsive PLGA nanoparticles through nanoprecipitation of PLGA and PEG-DSPE for co-delivery of DOX and perfluoro-octyl bromide (PFOB), a reinforcing agent to strengthen the cavitation effect of HIFU [164]. The resulting nanoparticles demonstrated improved BBB transportation and glioma accumulation by 17 and 13.4-fold relative to unmodified DOX-loaded nanoparticles, respectively. Hence, ANG-tethered nanomedicines with HIFU irradiation induced longer survival in orthotopic U87MG glioma-bearing BALB/c nude mice compared to unmodified DOX-loaded

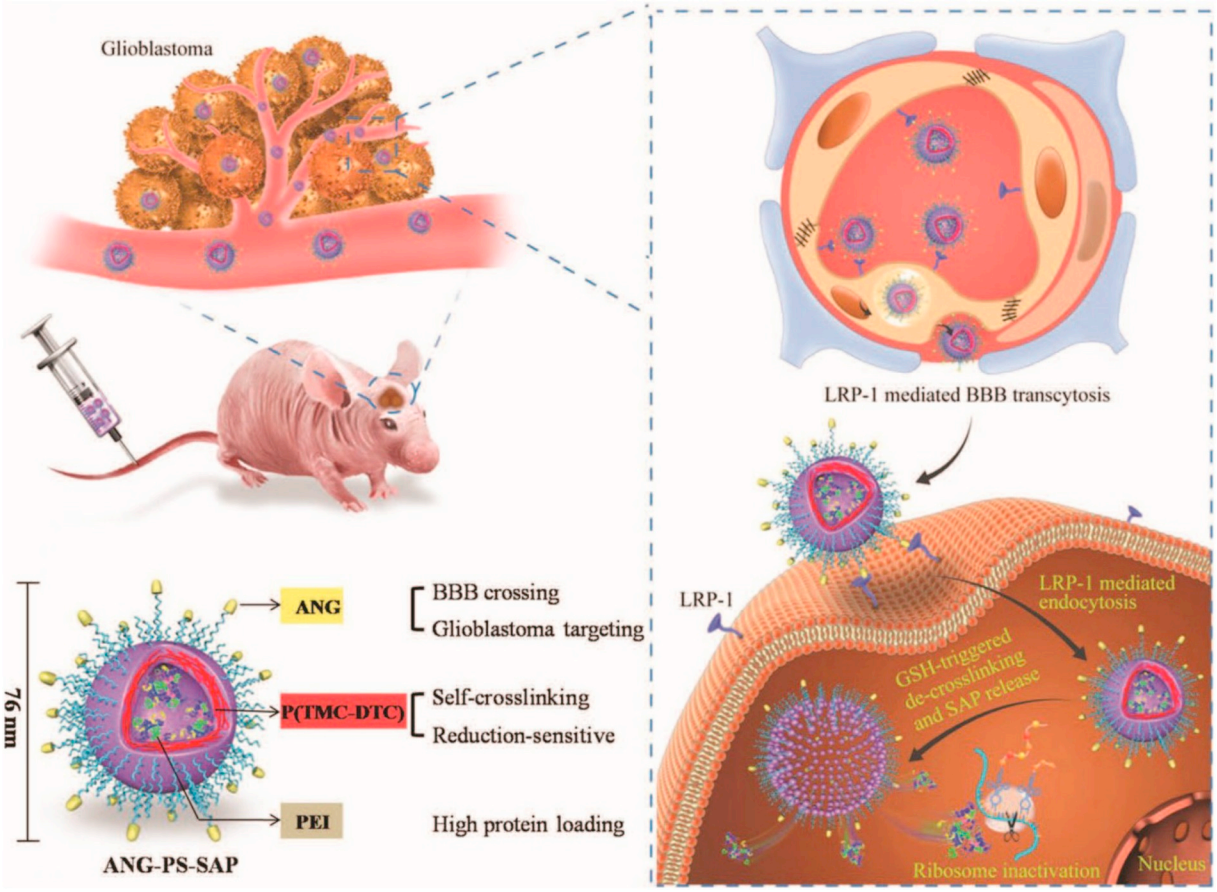


Fig. 4. Illustration of ANG-directed and redox-responsive virus-mimicking polymersomes (ANG-PS) for efficient loading and selective chaperone of SAP to orthotopic human glioblastoma xenografts in nude mice. Reproduced with permission from ref [167].

nanoparticles, with median survival times of 56 versus 23 days. Similarly, ANG decoration also enhanced the cytotoxicity of DOX-loaded polymersomes based on poly(dimethylsiloxane)-*b*-poly(2-methyloxazoline) diblock copolymers and PAMAM-PEG/DOX conjugates in U87MG and C6 cells, respectively [165,166]. ANG-directed and redox-responsive virus–mimicking polymersomes (ANG-PS) based on PEG-P(TMC-DTC)-PEI triblock copolymer efficiently and selectively chaperoned saporin (SAP), a potent natural protein toxin, to orthotopic human glioblastoma–bearing nude mice, leading to effective tumor suppression and significantly improved survival rate with little adverse effects (Fig. 4) [167]. ANG-modified PAMAM-PEG/pORF-TRAIL complexes extended the median survival time of orthotopic C6 glioma-bearing mice to 61 days, significantly longer than their non-targeted counterparts (30 days) [168]. Gao et al. conjugated ANG to bPEI-PLL-PEG copolymer that notably improved the BBB penetration of DNA by 9.7-fold compared to the unmodified control [169]. After complexation with therapeutic herpes simplex virus type I thymidine kinase gene (HSV-TK), ANG-modified systems induced over 3-fold higher tumor inhibition rate in an orthotopic U87MG mouse model than bPEI-PLL/HSV-TK complexes.

Given the fact that cRGD peptide binds to $\alpha_v\beta_3/\alpha_v\beta_5$ integrins overexpressed on both endothelial and glioma cells, which could facilitate BBB crossing and glioma targeting, several cRGD-decorated polymeric nanomedicines have demonstrated effective tumor inhibition of orthotopic U87MG glioma [79,82,85]. T7 peptide, with a sequence of CHAIYPRH and high affinity towards transferrin receptors on both BCECS and glioma cells, was introduced on the surface of carmustine-loaded PEG-PLGA micelles, leading to a better anti-glioma effect along with lower body weight loss and prolonged survival rate in orthotopic U87MG bearing BALB/c nude mice compared to the non-targeted control [170]. Ran et al. developed a WSW D-peptide (WSWGPYS), which endowed PTX-loaded PEG-PLA micelles with abilities of penetrating the BBB and targeting U87MG glioma, resulting in enhanced therapeutic efficacy [171]. Additionally, a brain tumor targeting peptide anti-SSTR2 peptide (AGCRNYFWKSFSSC) against somatostatin receptor 2 was reported to efficiently aid 3,3′-diindolylmethane-loaded PLGA nanoparticles to cross the in vitro BBB model and accumulate in orthotopic C6 glioma-bearing rats, inducing nearly complete tumor ablation [172].

Receptor-mediated endocytosis and transcytosis may stand as the underlying mechanism for peptide-modified nanomedicines listed above to cross the BBB. These BBB-crossing peptides all target to receptors that are highly expressed by endothelial and glioma cells, resulting in dual-targeting to both the BBB and glioma. Particularly, ANG peptide as the ligand of nanomedicines demonstrates obviously high BBB penetration and pronounced therapeutic effects in orthotopic mouse glioma models. This peptide-aided BBB bypassing strategy shows superiority over physical approaches including ultrasound, magnetic and osmotic barrier disruption, which are of relatively high cost and may cause tumor dissemination as well as neural damage.

8. Conclusion and perspectives

In recent years, peptides with diverse biological functions have been widely applied in optimizing polymeric nanomedicines for precision tumor therapy. Polymeric nanomedicines employing functional peptides can contribute to overcome major challenges in cancer therapy: (i) self-peptide prolongs the circulation time of nanoparticles *in vivo* at least better than PEGylation, and may thus enhance tumor accumulation; (ii) tumor tissue penetration peptides increase the concentration and penetration depth of nanomedicines in the tumor, achieving improved therapeutic efficacy; (iii) Tumor cell targeting and penetration peptides boost the tumor cell internalization of polymeric nanomedicines, resulting in higher intracellular drug concentrations and efficient tumor growth inhibition; (iv) endosomal escape peptides facilitate cytosolic delivery of polymeric nanomedicines, improving antitumor performance; (v) BBB crossing peptides aid BBB penetration and glioma accumulation of polymeric nanomedicines, enhancing the anti-glioma effect. As a result, peptide-functionalized systems in general exhibit superior antitumor efficacy with lower systemic toxicities both *in vitro* and *in vivo* compared to their non-peptide counterparts. Moreover, dual or multi-peptides have been simultaneously introduced onto the polymeric nanomedicines to achieve synergistic effects via either dual-ligands targeting [173–175] or combination of tumor cell penetration with tumor tissue penetration [176,177], tumor cell targeting [178–180] as well as BBB crossing and glioma targeting [181], which have demonstrated enhanced therapeutic effects over single peptide modified systems.

It should be noted, however, that the improvement in tumor therapeutic benefits of polymeric nanomedicines upon peptide functionalization was only several fold in tumor bearing mice. This is likely due to the fact that most of the peptide-decorated systems only partly address the problems in the drug delivery cascade, such as circulation, tumor accumulation and penetration, tumor cell uptake, endosomal escape or intracellular drug release. It's important to point out that the simultaneous accomplishment of the five steps cascade are cornerstones for a single drug delivery system to gain best performance. Hence, we should aim for the design of “all function in one” polymeric systems for cancer treatment. Aside from the effective therapy, safety is another big concern for polymeric nanomedicines to be approved for clinical trials. In this sense, polymeric nanocarriers have to be fabricated from safe and well-recognized biocompatible and biodegradable materials (polyesters, polycarbonates, polypeptides, PEG, natural polysaccharides etc.) in the future. Additionally, the physicochemical properties of nanosystems (size, shape, surface chemistry, stiffness and density of targeting ligands) can influence their biological performance and thus therapeutic outcomes as well.

In order to promote polymeric nanomedicines into the clinic, it's of paramount importance to engineer multifunctional polymeric nanosystems with good biocompatibility and biodegradability, high drug loading, long circulation time, efficient tumor accumulation and penetration, specific targeting capability and fast intracellular drug release. Strategies to synthesize peptide-functionalized polymers in advance before forming the nanomedicines should also be explored. In this way the surface concentration of the peptide on the nanosystems may be controlled in a better way and the fabrication process can be simplified, providing that the assembly process is not disturbed by the presence of the peptide. Cost-effectiveness is another important factor to be considered for the clinical translation. In the future, advantages of increased therapeutic efficacy have to be combined with efforts to decrease the complexity of the systems, to provide a reliable production process, to carefully investigate the safety aspects and to decrease the costs of the manufacturing of the nanosystems in order to facilitate clinical translation. We expect that with rational design and continuous studies based on deeper understanding of challenges faced by cancer nanomedicines, peptide–directed polymeric nanomedicines will become a reliable strategy for cancer treatment.

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