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Recent Research Progress of RGD Peptide–Modified Nanodrug Delivery Systems in Tumor Therapy

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Abstract

There have been great advancements in targeted nanodrug delivery systems for tumor therapy. Liposomes, polymeric nanoparticles, and inorganic nanoparticles are commonly employed as nanocarriers for drug delivery, and it has been found that arginine glycine aspartic acid (RGD) peptides and their derivatives can be used as ligands of integrin receptors to enhance the direct targeting ability. In this paper, we review the recent applications of RGD-modified liposomes, polymeric nanoparticles, and inorganic nanocarriers in cancer diagnosis and treatment, discuss the current challenges and prospects, and examine the progress made by the latest research on RGD peptide–modified nano delivery systems in cancer therapy. In recent years, RGD peptide–modified nanodrug delivery systems have been proven to have great potential in tumor therapy. Finally, we provide an overview of the current limitations and future directions of RGD peptide–modified nano-drug delivery systems for cancer therapy. This review aims to elucidate the contribution of RGD peptide–modified nanodrug delivery systems in the field of tumor therapy.

Keywords Cancer · Integrin · Nanocarrier · RGD peptide · Targeted drug delivery

Introduction

RGD was first identified as the minimal recognition sequence in fibronectin by Pierschbacher and Ruoslahti (1984). This sequence was then found in the adhesive extracellular matrices of other cells and has been described as a common cell recognition motif (Auzzas et al. 2010). RGD is an oligopeptide with a high affinity to the transmembrane heterodimer αvβ3 integrin receptor, which is overexpressed on activated neoplastic endothelium. Since its introduction and first application in the 1980s, it has been used as a standard tumor angiogenesis targeting ligand (Kunjachan et al. 2015); integrin-bound RGD peptide has had a great impact in the medical, biological, and biophysical sciences, and the design and use of synthetic integrin ligand have attracted much attention. Most of the current research focuses on the discovery of novel integrin-selective ligands and their applications in drug delivery, tumor therapy, and tissue engineering. Integrins are essential for a variety of biological functions and can also be used as imaging biomarkers to evaluate the efficacy of antiangiogenic and antitumor drugs (Desgrosellier and Cheresh 2010). RGD targets integrins αvβ3, α5β1, and αibβ3, which play a crucial role in tumor growth, metastasis, and angiogenesis. Integrins α1β1, α2β1, α5β1, α4β1, αvβ3, and αvβ5 have been shown to play an important role in regulating tumor angiogenesis. Antagonists of integrins αvβ3, α5β1, αvβ5, and α6β4 have shown great promise as potential inhibitors of tumor growth, metastasis, and angiogenesis (Desgrosellier and Cheresh 2010).

At present, many of the newly discovered RGD-binding integrin drugs have focused on integrin αvβ3 for the treatment of cancer (Desgrosellier and Cheresh 2010), ophthalmological diseases (Friedlander et al. 1996), and bone diseases (Nakamura et al. 2007) (RGD simulators and blocking antibodies to αvβ3 integrin have been shown to inhibit bone resorption in vitro and in vivo, indicating that this integrin may play an important role in regulating osteoclast function (Nakamura et al. 2007)). αvβ3 integrin

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is preferentially expressed in angiogenic endothelial cells (Brooks et al. 1994). Inhibition of integrin αvβ3 by antibody, RGD-based cyclic peptide, or nonpeptide mimics inhibits tumor angiogenesis. Antagonists of integrins αvβ3, α5β1, αvβ5, and α6β4 can act as potential inhibitors of tumor growth, metastasis, and tumor angiogenesis (Jin and Varner 2004). Although the safety of molecules targeting αvβ3 integrin is generally acceptable, they are seldom applied in the treatment of cancer because of their low treatment efficacy (Alday-Parejo et al. 2019). Integrin αvβ3 has been the most studied integrin over the last two decades, and inhibitors of RGD-binding integrin αIIbβ3 were among the first to be developed; these include tirofiban (Aggrastat), eptifibatide (Integrilin), and the antibody Abciximab (ReoPro), which are used to treat acute coronary syndrome and thrombotic cardiovascular disease (Slack et al. 2022).

Previous studies have shown that integrins exert their antitumor effects in the following manners (Duro-Castano et al. 2017): (i) promotion of antiangiogenesis by blocking the action of integrin through antagonists (Brooks et al. 1994; Desgrosellier and Cheresh 2010; Weis and Cheresh 2011a); (ii) blocking tumor metastasis in specific organs through the exosomal integrin (Hoshino et al. 2015); and (iii) delivering biologics/imaging agents directly to tumor sites by ligand targeting (Marelli et al. 2013). RGD is extensively used in cancer treatment as a specific identification site for the interaction of integrins with their ligands (Wang et al. 2013). Nanoparticles enter solid tumors through interendothelial gaps (Gerlowski and Jain 1986; Matsumura and Maeda 1986; Peer et al. 2007) and transendothelial pathways (Feng et al. 1999, 2002) in tumor vessels, which suggests that nanoparticles can be applied in the treatment of solid tumors (Sindhwani et al. 2020). The term nanodelivery system refers to the use of various complex materials to form nanoscale particles with encapsulated tumor therapeutic drugs to passively or actively target organs passively (Zhu et al. 2021). The particle size of the nanomedicine can be specifically designed in accordance with delivery requirements. By changing the size of the nanomedicine (Hu et al. 2021; Liu et al. 2019, 2020b), it can be delivered to different target sites such as tumor and lymph node (Jia et al. 2021; Yu et al. 2020a, b).

After appraising peer-reviewed published papers, we found that RGD peptides were commonly used to modify nanodrug delivery systems. As a ligand, RGD specifically recognizes membrane receptors on tumor cells, leading to the improved antitumor therapeutic effect of the drug and reduced toxic and side effects. In this review, we elucidate the interaction between RGD peptide and integrin αvβ3, summarize the applications of RGD peptide–modified liposomes and polymeric and inorganic nanoparticles in tumor therapy, and discuss the safety, current challenges, and development prospects of RGD peptide.

Structure and Function of RGD

Structure of RGD

RGD (Fig. 1) is the basic binding motif of at least seven integrin receptors (Hynes 2002; Tamkun et al. 1986). RGD peptides can be linear or cyclic. Cyclic RGD peptides display a higher activity compared to linear RGD peptides due to their more stable conformation that resists proteolysis (tomograph 2007; Verrier et al. 2002). The specificity of the RGD peptide depends on the backbone conformation, the charged side chains of the Arg and Asp residues, and the hydrophobic moieties of the flanks of Asp residues (Schaffner and Dard 2003). The RGD motif's freedom of conformation determines its binding strength to the integrin, and molecular dynamics simulations have shown that while RGD motifs are mostly exposed to solvents that can be bound in all synthetic systems, their flexibility depends on the refined geometry (Le et al. 2017). The interaction between the RGD peptides and integrin αVβ3 is influenced by direction and distance (Dong et al. 2017). Monomer RGD peptide is taken up by cells in an unspecific manner, whereas poly RGD peptide is thought to be internalized via integrin-mediated endocytosis. Kemker et al. (2020) demonstrated the potential correlation between the cellular uptake mechanism and molecular mass by double derivation of peptide c(RGDw(7Br)K). This suggests that PEG coupling can cause integrin-mediated endocytosis of monomeric RGD peptide.

Fmoc-chemistry solidiphase peptide technology is commonly used in RGD synthesis (Li et al. 2020a; Dechantsreiter et al. 1999) created n-methylated Cyclo(GDF-N (Me) V-) using Merrifield solid-phase peptide technology. Thumshirn et al. (2003) synthesized a polymeric cyclic c(-RGDfE-)-peptide and a cyclic pentapeptide ring

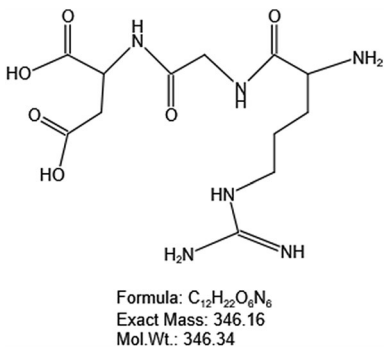

Fig. 1 Structure of Arg–Gly–Asp (RGD)

(-Arg[Pbf]GlyAsp[t Bu] -D -PheGlu-) by a solid-solution method, Cyclo(-RGDfK-) peptide. Kim et al. (2017b) synthesized RGD using solid-phase peptide technology.

Mechanism of RGD Peptide's Targeted Binding to Integrin

Yu et al. (2014) conducted molecular dynamics simulations to further investigate the effect of the structure and quantity of RGD peptides on the molecular targeting mechanism of RGD-containing peptides and integrin αVβ3. Electrostatic interactions between RGD residues and metal ions in integrin V3 are primarily responsible for target recognition. Cyclic RGD peptides bind to integrin V3 more strongly compare to linear RGD. Furthermore, the optimal molar concentration ratio of RGD peptides to integrin αVβ3 appears to be 2:1, and the RGD peptide plays a key role in targeted anticancer drug delivery as an integrin αVβ3–targeting peptide (Yu et al. 2014). Both linear and circular RGD (cRGD) peptide sequences bind to integrins αvβ3 and α5β1 (Kapp et al. 2017; Liu 2009), which is important in tumor therapy (Danhier et al. 2012; Howe and Addison 2012).

Kapp et al. (2017) demonstrated that the key to binding of αIIbβ3 to RGD is to replace the guanidine group in the ligand with an amine. As shown in Fig. 2, the guanidine group binds to the α-subunit via a forked salt bridge in all RGD-binding isoforms, except for αibβ3. Linear RGD ligand and the guanidine group of Arg form a bidentate salt bridge by binding laterally to the αvβ3 of α-subunit Asp218. In addition to this lateral interaction (Asp227 in α5), an end-to-end interaction between guanidine and Gln221 has been observed in the crystal structure of α5β1.

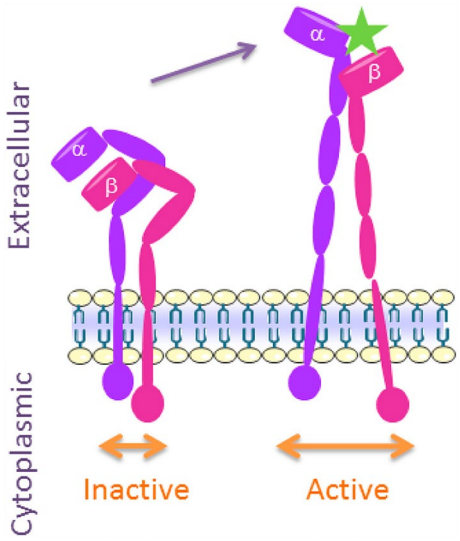

Fig. 3 Conformational changes of αvβ3 integrin. After activation, the extracellular domain extends and straightens to reveal the RGD-binding domain (star shape); reproduced with permission (Danhier et al. 2012)

It is generally accepted that most integrins, including those expressed on endothelial cells, have "on" and "off" states, as illustrated in Fig. 3. The extracellular domain of αvβ3 integrins is bent or folded, thereby concealing the RGD-binding site and preventing ligand binding, whereas the extracellular domains of RGD-bound αvβ3 integrins are unbent or straight (Danhier et al. 2012).

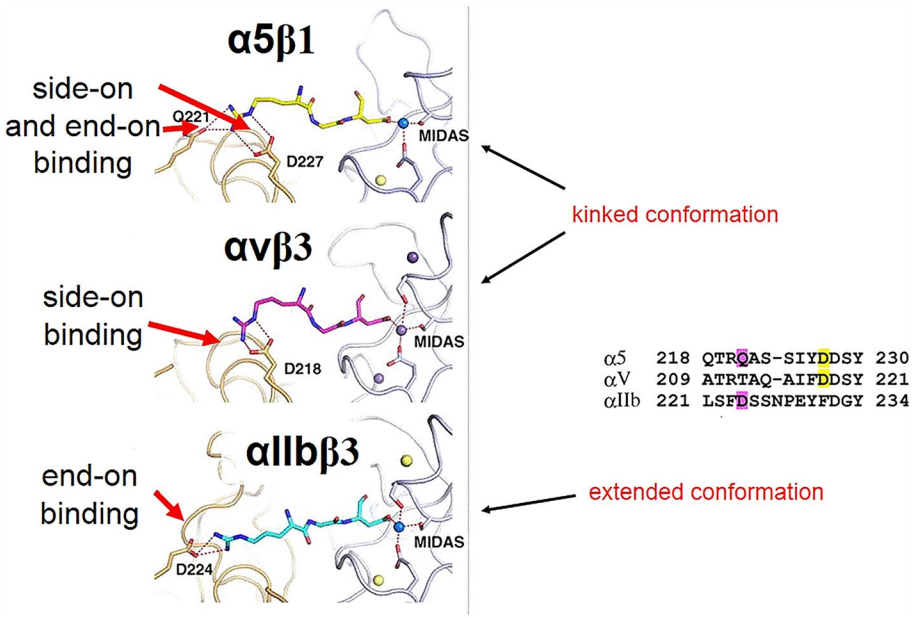

Fig. 2 Different binding modes of linear RGD peptides to different integrin subtypes. Crystal structures of α5β1 (top), αvβ3 (middle), and αIIbβ3 (bottom) in complex with RGD ligands; reproduced with permission (Kapp et al. 2017)

RGD-Targeted Nanodrug Delivery System

As one of the most important drug delivery systems, nanomedicine systems play a crucial role in tumor therapy (Farokhzad and Langer 2009). Integrins are important in tumor growth, which makes them attractive targets for tumor therapy (Desgrosellier and Cheresh 2010). Integrin antagonists inhibit tumor growth by affecting tumor cells and tumor-associated host cells, particularly angiogenic endothelial cells. Integrin antagonists, including monoclonal antibodies and RGD peptidomimetics, are currently being evaluated in clinical trials (Avraamides et al. 2008). RGD has a high affinity for integrin (Kunjachan et al. 2015). Therefore, an RGD-functionalized nanodrug delivery system can deliver therapeutic drugs with a significant antitumor effect. RGD peptide is the most commonly used tripeptide that can specifically bind to integrin receptors overexpressed in tumor cells (Kunjachan et al. 2015); therefore, peptides that contain the RGD sequence are regarded as ideal targeting moieties for nanocarriers. RGD can be used to modify liposomes, micelles, and inorganic or organic nanoparticles (Hu et al. 2016). Here, we discuss the latest relevant examples of RGD-functionalized nanodrug delivery systems, such as RGD-modified liposomes, polymers, and inorganic nanoparticles.

Lin et al. (2019) prepared c(RGDfC)-modified Doxorubicin(DOX)-loaded polypeptide vesicles using the emulsion solvent evaporation technique. The vesicles exhibited higher tumor inhibition rates and lower toxicity compared with free DOX, indicating that RGD-modified nanomedicine formulations have great potential in the field of tumor therapy. Li et al. (2020a) synthesized Ptx-SA-RGD conjugates and demonstrated that the RGD-modified nanofiber delivery system improved the antitumor effect of the drug. Fei et al. (2017) prepared RGD-conjugated and lipid-coated silicon dioxide nanomaterials (RGD-LP-CHMSN-ATO) through self-assembly technology and improved film hydration method; they showed that the RGD-modified nanodrug delivery system can be used in tumor therapy and enhance antitumor effects. Hu et al. (2015) successfully constructed NAMI-A@MSN-RGD with the coupling reaction and lyophilization technology. The results showed that NAMI-A@MSN-RGD enhanced the antiangiogenesis effect and inhibited cell proliferation, migration, invasion, and capillary formation. Peng et al. (2020) discovered that iRGD-modified (PCL-b-PVP) nanoparticles exhibited excellent tumor penetration in a mouse subcutaneous xenograft model. nRGD-modified DOX-loaded liposomes showed superior antitumor efficiency compared with PEG-modified DOX liposomes, indicating that RGD-modified nanodrug delivery systems can be used to improve tumor penetration, which makes them attractive as a potential nanodrug delivery system in the field of tumor therapy. Nanoparticle accumulation in tumors can improve the efficacy of antitumor therapy, peptide ligands on nanoparticles provide affinity for receptors on cancer cell surface, and peptide-functionalized nanoparticles can actively target cancer cells, leading to enhanced antitumor therapy (Fernandes et al. 2015; Long et al. 2020) developed RGD-HSA-RVT nanoparticles for the treatment of ovarian cancer using a high-pressure homogenizer and emulsion solvent evaporation method. The RGD-HSA-RVT nanoparticles demonstrated a high tumor inhibition rate. Xu et al. (2017) modified nanoparticles with iRGD peptide to promote the penetration of nanoparticles into tumor tissues and their accumulation in tumor cells.

In general, RGD-targeted nanodrug delivery systems can improve chemotherapy drug efficacy, reduce side effects, and improve antitumor efficiency (Hu et al. 2015; Li et al. 2020a; Lin et al. 2019; Wei et al. 2020). The high affinity between RGD and αv integrin promotes tumor cell uptake of RGD-modified nanomaterials, thereby enhancing tumor penetration of RGD-modified nanomaterials (Peng et al. 2020) and improving antitumor efficiency (Fernandes et al. 2015).

RGD-Modified Liposomes

Liposomes are nanophospholipid bubbles with a lipid bilayer. They can prevent rapid drug degradation and reduce toxicity when lipophilic/hydrophilic drugs are incorporated (Bulbake et al. 2017; Torchilin 2005). By utilizing the unique properties of liposomes, the drug efficacy can be enhanced by increasing metabolism and absorption, reducing elimination rate, and extending biological half-life (Estanqueiro et al. 2015; Kesharwani et al. 2021).

RGD-modified liposomes are still in an early development stage for targeted mediated therapy. To date, they have received little attention in clinical trials. However, RGD-modified liposomes have the ability to target cancer cells and release drugs in precise and necessary ways for cancer treatment (Sheikh et al. 2022). As previously stated, RGD peptides are capable of recognizing integrins, and integrins are overexpressed in many cancers. Therefore, many researchers have sought to combine the benefits of RGD with the properties of liposomes to create RGD-functionalized liposomes in order to study the effect of RGD-functionalized liposomes on tumor growth. The applications of RGD-modified liposomes in tumor therapy are shown in Table 1.

Table 1 RGD-modified liposome formulations

Binding motif	Preparation method	Formulation	Cancer/cancer cell type	Particle size (nm)	Zeta-potential (mV)	References
RGD	Thin-film hydration and extrusion	MC-T-DOX	Pancreatic cancer	100.00	–	Wei et al. (2020)
cRGDfK	Lipid film hydration method	RGD-PEG-LPs	OSRC-2 cells	127.00 ± 2.00	− 19.00 ± 3.00	Kibria et al. (2013)
cyclic RGD	Solvent injection method	RGD-MEND	Renal cell carcinoma	115.00 ± 10.00	− 18.00 ± 4.00	Sakurai et al. (2014)
RGD	Solvent evaporation method	RGD-modified PTX-CUR LPs	A549	120.6 ± 10.83	− 5.62 ± 1.13	Jiang et al. (2018a)
RGD	The thin-film hydration method	RGD-liposomal EPO906	rhabdomyosarcoma	100.00	–	Scherzinger-Laude et al. (2013)
RGD	The thin-film hydration method	RGD-SSLs-SHK	Breast cancer	117.53 ± 3.05	− 15.37 ± 0.91	Wen et al. (2018)
DSPE-PEG2000-RGD	The thin-film hydration method	DSPE-PEG2000-RGD-LPs/QCT	A549	93.90 ± 6.20	− 21.50 ± 0.40	Zhou et al. (2018)
RGDm	The film dispersion method, ultrasonication disperse and extrusion	RGDm-SSL-DOX	Melanoma B16 tumors	120.00	–	Xiong et al. (2005)
RGD	The thin-film hydration method	RGD-SSL-PTX	The SKOV-3 human ovarian cancer cell line	120.00	–	Zhao et al. (2009)
RGD	The thin-film hydration method	RGD-LP-PTX	PC-3 cells	95.00 ± 6.40	− 2.63 ± 1.17	Cao et al. (2015)
RGD	The thin-film hydration method	EPO906-RGD-liposomes	Neuroblastoma and rhabdomyosarcoma	100	–	Scherzinger-Laude et al. (2013)
RGDm7	The lipid film hydration method	50R-LIPO-DOX; 50R10D-LIPO-DOX	Circulating tumor cells (CTCs)	99.70 ± 1.02; 112.40 ± 2.55	− 24.30 ± 0.65; − 27.70 ± 0.46	Song et al. (2020)
cRGD, RGDf[N-Met]C	Lipid film hydration and extrusion method	RGD-Dox-TSL	B16Bl6 (murine melanoma) cells	85.00	–	Dicheva et al. (2015)
RGD	Freeze-drying method					Majzoub et al. (2014)

RGD-Modified Polymeric Nanoparticles

Polymeric drug delivery systems have grown in popularity since 1960 (Kamaly et al. 2016). Polymer-based nanocarriers with polymer properties and colloidal sizes are classified as (i) polymer micelles, (ii) polymeric objects, (iii) polymer hydrogels, and (iv) polymer dendrimers (Andreu and Arruebo 2018; Chen et al. 2017; das Neves et al. 2015; Kamaly et al. 2016). RGD-modified polymers in combination with αvβ3 integrins have been extensively studied for tumor therapy (Cheng and Ji 2019). Polymeric nanoparticles composed of natural materials, semi-synthetic polymers, and synthetic polymers have been extensively studied (Andreu and Arruebo 2018). The applications of RGD-modified polymer nanoparticles in tumor therapy are shown in Table 2.

Li et al. (2022) prepared Arg-Gly-Asp-d-Tyr-Lys(cRGDyK)-conjugated silicon phthalocyanine by covalently connecting RGD to silicon phthalocyanine. It was demonstrated that Arg-Gly-Asp-d-Tyr-Lys(cRGDyK)-conjugated silicon phthalocyanine had a great anti–breast cancer effect. The RGD peptide was covalently bound to the surface of carboxylate-functionalized carbon nanotubes (fCNT), and the topoisomerase I inhibitor camptothecin (CPT) was encapsulated in fCNT (CPT@fCNT-RGD). It was found that CPT@fCNT-RGD could be applied in targeted tumor therapy with a higher tumor inhibition rate (Koh et al. 2019; Xiao et al. 2012) prepared H40-DOX-cRGD- 64 Cu and discovered that H40-DOX-cRGD- 64 Cu exhibited a higher tumor inhibition rate in a xenograft tumor mouse model. Chen et al. (2017) prepared cRGD-SS-NGS by modifying polymer

Table 2 RGD-mediated polymeric nanoparticles

Binding motif	Preparation method	Formulation	Cancer/cancer cell type	Particle size (nm)	Zeta potential (mV)	Ref.
cRGDfK	Inverse nanoprecipitation, "click" reaction, and cRGD conjugation	cRGD-SS-NGs	U87-MG cells	142.00	–	Chen et al. (2017)
cRGDfC	Emulsion polymerization and cRGD conjugation	βCD-PAMAM-PEG-cRGD	U87-MG cells	35.00–54.00	–	Saraswathy et al. (2015)
cRGDfK	Self-assembly method and cRGD conjugation	NHAc-FI-PEG-RGD/DOX	U87-MG cells	5.40	20.40 (pH = 5), 0 (pH = 7), − 26.80 (pH = 10)	He et al. (2015)
cRGDfC	Organic synthesis	PAM-PBLG-b-PEG-cRGD	HepG2 cells	78.20	− 6.30	Tang et al. (2017)
iRGD	Hydration film method	iRGD-PS-PTX	MKN-45P and CT26 cells/Peritoneal carcinomatosis	233.00	− 2.70	Simón-Gracia et al. (2016)
RGD	Organic synthesis	RGD-PAMAM -ce6	A375 cells	28.00	0.80	Yuan et al. (2015)
cRGDfK	Chemical conjugation reaction	cRGD-gPEG-Ce6	SKOV-3/KB cells	3.00–4.00	− 6.00	Kim et al. (2017a)
RGD	Emulsion polymerization	RGD-DEPt	MDA-MB-231 cells	1.40	37.00	Zhou et al. (2016)
RGD	Lyophilization	RGD-modified Au PENPs	U87-MG cells	200.00–350.00	4.80–13.20	Kong et al. (2017)
RGD	The clip photochemistry methodology and RGD conjugation	C_{PEG} RGD	H1299 cells	191.00–211.00	–	Ragelle et al. (2015)
RGD	Organic synthesis	RPgWSC/pDNA	PC-3 cells	178.40	–	Kim et al. (2017b)
cRGD	cRGD conjugation	MN-anti-miR10b	MDA-MB-231 human breast adenocarcinoma cells	/	–	Yigit et al. (2013)
RGD	Covalent and conjugation	CPT@fCNT-RGD	A375 and MCF7 cells	5.04	–	Koh et al. (2019)
cRGD	Conjugation	H40-DOX-cRGD-^{64}Cu	U87MG human glioblastoma cells	65.00	–	Xiao et al. (2012)
RGD	Conjugation	Ptx-SA-RGD	Gastric cancer cells MGC803	1540.00–1760.00	−0.53	Li et al. (2020a)
RGD	Conjugation	RGD-tk-Epo B	PC-3, HCT116, and L929 cells	85.73	–	Xia et al. (2020)

nanogel with cRGD using reverse nanoprecipitation, "click" reaction, and cRGD coupling method. cRGD-SS-NGS was able to bind to v3 integrin, which was overexpressed in human glioblastoma U87-MG cells. This led to the targeted release of DOX and higher lethality against U87-MG cells.

In summary, RGD-modified polymeric nanoparticles are promising for improving the selective delivery of drugs to tumor tissues.

RGD-Modified Inorganic Nanoparticles

Even though inorganic materials are not biodegradable, due to their unique physical and chemical properties, they have advantages in drug delivery applications that include ease of preparation, versatility, good storage stability, and biocompatibility. Thus, inorganic materials are widely used to deliver various drugs (Andreu and Arruebo 2018). Because of their well-defined structure and biocompatibility, mesoporous silica nanoparticles can be used in tumor therapy (Luo et al. 2014; Shen et al. 2015; Xing et al. 2012). Furthermore, mesoporous silica nanoparticles with targeted

Table 3 RGD-mediated inorganic nanoparticles

Binding motif	Preparation method	Formulation	Cancer/cancer cell type	Particle size (nm)	Zeta potential (mV)	References
K_4YRGD	Atomization	MSN@Alg microspheres	HepG2 cells	20.00–30.00	–	Liao et al. (2014)
cRGD	Passive PEGylation and active cRGD conjugation	c-RGD-LPAgNPs	U87MG cancer cells	20.90 ± 4.60	− 30.00	Sun et al. (2014)
cRGD	Sol-gel method and cRGD conjugation	CPMSNs	Triple-negative breast cancer (MDA-MB-231)	65.00–75.00	+ 42.80	Murugan et al. (2016)
cRGDyK	cRGDyK conjunction	A647@MSN-RGD-PdTPP	MCF-7 and U87-MG cells	100.00	–	Cheng et al. (2010)
N 3 -GRG-DSGRGDS-NH 2	Sol-gel method and synthesis of peptide-capped MSNs via	DOX@MSN-SS-RGD	U87 MG and COS 7 cells	100.00	+ 24.30	Li et al. (2015)
RGD	RGD conjugation	RGD-LP-CHMSN	HepG2, MCF-7 and LO2 cells	100.67 ± 1.14	35.00 ± 0.75	Fei et al. (2017)
RGD	One-pot synthesis	GTe-RGD	A375	220.00	–	Huang et al. (2020)

peptides have been extensively studied for drug delivery (Chen et al. 2016; Hu et al. 2016; Yang and Yu 2016).

Murugan et al. (2016) used the sol-gel method and cRGD coupling to prepare CPMSN by loading topotecan (TPT) and quercetin (QT) into 65–75 nm mesoporous silica nanoparticles modified with polyacrylic acid (PAA)/chitosan (CS) containing cRGD. CPMSN was applied for the treatment of breast cancer. Cheng et al. (2010) prepared A647@MSN-RGD-PdTPP nanoparticles with a high affinity for αvβ3 integrin on cancer cells, which can be used for tumor therapy. The applications of RGD-modified inorganic nanoparticles in tumor therapy are shown in Table 3.

In summary, RGD peptide exhibits excellent specific binding ability for αvβ3 integrin. Furthermore, RGD-modified polymer and liposome nanovehicles and inorganic nanoparticles have been extensively studied in the field of drug delivery systems for cancer therapy, especially for chemotherapy. In this context, many outstanding results have been achieved, demonstrating that RGD-modified polymers, liposomes, and inorganic nanoparticles have broad application prospects and enormous development value as nanovehicles. With rapid developments in molecular biology, genetic science, pharmacy, and other related disciplines, there will surely be comprehensive and in-depth research with regard to applications of RGD-modified polymers, liposome nanovehicles, and inorganic nanoparticles in the field of cancer treatment.

Effects of RGD on Adhesion and Migration of Tumor Cells

RGD is the smallest cell adhesion peptide sequence found in fibronectin (Pierschbacher and Ruoslahti 1984). Not only can RGD initiate cell adhesion, but it can also selectively process certain cell reactions. The motif of the RGD peptide, its density, and arrangement on the surface contribute to successful cell attachment. In addition, RGD can influence specific cellular behavior (Hersel et al. 2003). Appropriate RGD-modified nanomaterials can inhibit tumor metastasis by inhibiting cell migration (Liu et al. 2020a). Furthermore, RGD can be specifically recognized and bound by integrin to inhibit the integrin signaling pathway and prevent tumor cell adhesion, migration, invasion, and proliferation, resulting in antitumor effects (Yang et al. 2021). RGD peptide can bind to integrin receptors competitively and inhibit tumor cell migration (Yang et al. 2021). rLj-RGD3 can block the adhesion, migration, and invasion of ovarian cancer cell line HeyA8 (Zheng et al. 2017; Wen et al. 2018) synthesized RGD-SSLs-SHK for the treatment of breast cancer, they found that in comparison with SSLs-SHK, RGD-SSLs-SHK inhibited cell proliferation, migration, invasion, and adhesion by lowering MMP-9 expression and NF-B p65 levels.

RGD-Induced Tumor cell Apoptosis

RGD peptide can induce apoptosis in a dose-dependent manner, thereby inhibiting the proliferation of endothelial cells (Hamdan et al. 2019). RGD peptide–modified and DOX-loaded selenium nanoparticles (RGD-NPs) are

a nanodelivery system capable of inducing apoptosis and cell cycle arrest in Human Umbilical Vein Endothelial Cells(HUVECs) (Fu et al. 2016). rLj-RGD3 can inhibit the proliferation of ovarian cancer cell line HeyA8 by inducing apoptosis (Zheng et al. 2017; Wen et al. 2018) synthesized RGD-SSLs-SHK for the treatment of breast cancer; when compared with SSLs-SHK, RGD-SSLs-SHK induced cell apoptosis by decreasing Bcl-2 expression and increasing Bax expression. Babu et al. (2017) prepared PLGA-CNP-RGD, which triggered more lung cancer cell apoptosis and induced G2/M cell cycle arrest compared with nontargeted preparations.

RGD Inhibits Tumor Angiogenesis

Angiogenesis plays an important role in the occurrence and development of a variety of tumors. Angiogenesis imaging can help with early tumor detection and treatment response assessment.

RGD has a high affinity for the transmembrane heterodimer αvβ3 integrin receptor, which is overexpressed on activated neoplastic endothelial cells. Thus, the tumor vascular endothelium is damaged after active (vascular) targeting of the αvβ3 integrin receptor by gold nanoparticles and subsequent irradiation (Kunjachan et al. 2015). RGD peptide can recognize and specifically bind αvβ3 and αvβ5 integrins, which contribute to tumor vascular system accumulation or their associated binding (David 2017; Kapp et al. 2017).

Thumshirn's team synthesized the first synthetic, highly active, and selective αvβ3 receptor antagonist, cyclo (-RGDfV-), and derivation resulted in an N-alkylated cyclic peptide ring (-RGDf[NMe]V-) that has entered Phase II clinical trials as an angiogenesis inhibitor (Cilengitide, code EMD 121,974, Merck) (Thumshirn et al. 2003). This derivate inhibits tumor migration and angiogenesis by utilizing RGD competitively binding to integrin receptors (Yang et al. 2021).

In addition, RGD-functionalized nanomaterials inhibit angiogenesis by promoting cell apoptosis, and the strategy of using RGD-functionalized Mesoporous silica nanoparticles(MSNs) as NAMI-A carrier is an effective way to enhance cancer-targeted antiangiogenesis (Hu et al. 2015; Hood et al. 2002) highlighted antiangiogenic therapy targeting αvβ3 via nonpeptide mimetics of RGD coupled to nanoparticles. Hida et al. (2016) delivered VEGFR2 siRNA by using RGD-MEND nanoparticles to inhibit tumor growth by antiangiogenesis. RGD-modified D (KLAKLAK) 2 can specifically bind to αvβ3 integrin receptor overexpressed on tumor endothelial cell surface, leading to the death of endothelial cells and destroying tumor blood vessels, thereby inhibiting tumor cell growth (Ellerby et al. 1999; Smolarczyk et al. 2006).Researchers have constructed a fusion protein containing prothrombin and the αvβ3 endothelial cell receptor (tCoa-RGD), and injection of tCoa-RGD caused extensive thrombus formation in a mouse xenograft tumor model, leading to extensive tumor necrosis (Jahanban-Esfahlan et al. 2017; Fu et al. 2016) prepared RGD-modified and DOX-loaded selenium nanoparticles (RGD-NPS), which could induce apoptosis and cell cycle arrest in HUVECs, thereby inhibiting MCF-7 tumor growth and tumor angiogenesis in nude mice.

In summary, with regard to the mechanism of RHD in tumor treatment, we can conclude that RGD inhibits the regeneration and migration of tumor cells by affecting tumor cell adhesion and migration, and inhibits the growth of tumor cells by inducing tumor cell apoptosis and inhibiting tumor angiogenesis.

Application of RGD in the Treatment of Various Tumors

Because RGD can recognize integrin αvβ3, a series of RGDs have been synthesized for tumor cell targeting. As previously mentioned, integrin αvβ3 is expressed on angiogenic blood vessels and tumor cells, and it plays an important role in tumor growth, metastasis, and angiogenesis. Thus, the development of RGD peptide–functionalized nanodrug delivery systems has a promising future in the field of tumor therapy (Fu et al. 2019). Table 4 summarizes the antitumor effects of RGD.

Exogenous RGD peptide effectively inhibits the binding of ligand and integrin, thereby inhibiting tumor cell angiogenesis and migration, and it can also be used to mark tumors and deliver anticancer drugs (Danhier et al. 2012; Garanger et al. 2007; Zitzmann et al. 2002). In comparison with NC@PDA-PEG or free paclitaxel, NC@PDA-PEG-RGD can better promote drug accumulation in the tumor and thus better inhibit tumor growth, indicating the superiority of RGD peptide–modified nanodrug delivery system therapy in lung cancer (Huang et al. 2019).

In conclusion, RGD-functionalized nanoparticles have the potential to inhibit tumor cell proliferation, migration, invasion, and adhesion, and RGD-modified nanodrug delivery systems have the potential to target drug delivery. Thus, using RGD-modified nanodrug delivery systems to achieve targeted cancer therapy is a very promising approach. RGD peptide and its derivatives–functionalized nanoparticles have widely been used in cancer therapy.

Twelve RGD-targeted drugs have been studied in clinical trials since 2006. Cilengitide (an RGD-containing integrin antagonist) (Feng et al. 2014) has been developed as a cancer therapeutic agent, and phase I clinical trials have revealed its

Table 4 RGD-Targeted agents are used in cancer therapy

Binding motif	Loaded drug	Components	Cancer/cancer cell type	References
RGD	Cisplatin	CPFT-RGD	A549	Yadav et al. (2023)
cRGD	Camptothecin (CPT)/DOX/DOX	CPT@fCNT-RGD/H40-DOX-cRGD/RGD-SPIO@MSN NPs	A357/ U87MG/ HepG2	Koh et al. (2019); Xiao et al. (2012); Zhao et al. (2023)
N-Methylated cyclic RGD	miRNA	MN-anti-miR10b	MDA-MB-231	Yigit et al. (2013)
RGD	Paclitaxel	NC@PDA-PEG-RGD	A549	Huang et al. (2019)
c(RGDfE)	Gemcitabine	c(RGDfE)–pMMSNs	BxPC-3	Sun et al. (2015)
RGDm7	Doxorubicin (DOX)	R-LIPO, D-LIPO and RD-LIPO	Jurket cells	Song et al. (2020)
RGD	Epothilone B	RGD-tk-Epo B	Human prostatic cancer cell line (PC-3)	Xia et al. (2020)
RGD	Paclitaxel (Ptx) and tetrandrine (Tet)	Ptx-SA-RGD and P/T-NFs	The gastric cancer cell line MGC-803	Li et al. (2020a)
RGD	Doxorubicin and cilengitide	MC-T-DOX	BxPC-3	Wei et al. (2020)
RGD	Camouflaged graphene oxide quantum dots (GOQDs), doxorubicin, and Gamabufotalin	GTDC@MR NPs	Triple-negative breast cancer (TNBC)	Fan et al. (2020)
RGD	Doxorubicin (DOX)	RGD-PCD/DOX NPs	HepG2	Huang et al. (2014)
cRGD-PEG2000-DSPE	Paclitaxel (PTX)	RGD-KLA/PTX-Lips	4T1 tumor	Sun et al. (2017)
RGD	Arsenic trioxide	RGD-LP-CHMSN-ATO	H22 tumor	Fei et al. (2017)
cRGD	Gefitinib	R-RBC@GEF-NPs	A549	Wen et al. (2021)
RGD	Norcantharidin	RGD-LPH-NCTD	Triple-negative breast cancer (TNBC)	Li et al. (2019)
iRGD (internalizing RGD)	Hypocrellin B (HB)	HB-PA	Breast tumor	Jiang et al. (2018b)
RGD	Epothilone B (Epo B)	RGD-tk-Epo B	PC-3	Xia et al. (2020)
RGD	Tellurium (Te)	GTe-RGD	Breast cancer	Huang et al. (2020)
RGD	mTHPC	mTHPC@VeC/T-RGD NP	Colorectal cancer (CRC)	Yuan et al. (2021)
RGD	Gold nanoparticles (t-NP)	t-NP	Human pancreatic adenocarcinoma cell line Capan-1 (ATCC HTB-79)	Kunjachan et al. (2019)
cRGD	Doxorubicin (DOX)	H40-DOX-cRGD	U87MG	Xiao et al. (2012)
RGD	magnetosomes	Magnetosomes@RGD	The B16F10 melanoma cells	Hafsi et al. (2020)
RGDyc	Paclitaxel	NC@PDA-PEG-RGD	A549	Huang et al. (2019)
RGD	Paclitaxel	MSNs-NH 2 -FA-RGD	Human breast cancer cells MCF-7	Yan et al. (2020)
RGD	Gemcitabine	RGD-PEG3500-DSPE GEM LPs	Ovarian cancer (SKOV3 cells)	Tang et al. (2019)
RGD	Doxorubicin	Dox/P(RGD) NC	Ovarian cancer cells (CAOV-3 cells)	Hadad et al. (2020b)
RGD	Shikonin	(RGD-SSLs-SHK	Breast cancer	Wen et al. (2018)

favorable safety profile (Nabors et al. 2007) (https://www.clinicaltrialsregister.eu/ctr-search/search for "Cancer AND RGD"). (On November 22, 2022, the database was queried.)

RGD for Tumor Imaging and Diagnosis

Over the last few decades, several radiolabeled RGD peptides targeting integrin αvβ3 have been prepared and optimized for positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging (Liu and Wang 2013). RGD peptide can be used to modify the nanodrug delivery system for tumor imaging. cRGD cyclic peptide is a polypeptide with active targeting properties. A number of preclinical experiments have shown that cRGDyK combined with imaging agents (e.g., microvesicles, magnetic resonance contrast agents, fluorescein) (Guo et al. 2020; Zhang et al. 2017c, 2018) can effectively improve the sensitivity of contrast agents to tumor imaging.

Table 5 RGD drugs in clinical trials

Drug	Classification	Indications	Clinical trial phase	Date	NCT No.
68Ga-NODAGA-RGD PET/CT	Radiotherapy	Potential for neovascularization in patients following tumor pathology (pathological angiogenesis)	Phase 1	28th Jan. 2016–14th June 2022	NCT02666547
Ad5-Delta 24RGD	Adenovirus	Ovarian carcinoma, primary peritoneal carcinoma	Phase 1	21st Nov. 2007–26th Jan. 2011	NCT00562003
Ad5.SSTR/TK.RGD	Adenovirus	Ovarian carcinoma	Phase 1	25th Aug. 2009–13th Feb. 2013	NCT00964756
Delta-24-RGD-4 C	Adenovirus	Glioma	Phase 1	9th Dec. 2008–16th Jul. 2018	NCT00805376
Delta-24-RGD	Adenovirus	Glioma	Phase 1, Phase 2	20th Apr. 2012–9th Mar. 2015	NCT01582516
Delta-24- RGD and Temozolomide	Adenovirus	Glioma	Phase 1	8th Oct. 2013–24th Oct. 2017	NCT01956734
68Ga-AlfatideII	Radiotherapy	Lung cancer, tuberculosis	Phase 1, Phase 2	Mar. 2014–Oct. 2014	NCT02481726
DNX-2401 and Interferon gamma (IFN-γ)	Virus	Glioma	Phase 1	22nd Jul. 2014–16th Jul. 2018	NCT02197169
[F-18]RGD-K5	Molecular imaging tracer	Metastatic breast cancer; metastatic colorectal/rectal cancer; non-squamous non-small cell lung cancer	Phase 2	2nd Oct. 2009–22nd Aug. 2012	NCT00988936
RGD PET/CT	Molecular imaging tracer	Oropharyngeal squamous cell carcinoma	Phase 2	22nd Nov. 2019–1st Sep. 2023	NCT04222543
Flotegatide (18 F) or RGD (68Ga)	Radiotherapy	Advanced head and neck cancer; advanced non-small cell lung cancer	Phase 2	20th Mar. 2015–20th Sep. 2018	NCT02325349
DNX-2401	A transgenic oncolytic adenovirus	Glioma	Phase 2	14th Jun. 2016–15th Jul. 2021	NCT02798406
99mTc-3PRGD2	Radiodiagnostics preparation	Lung cancer	Phase 3	18th Jan. 2020–27th Apr. 2022	NCT04233476
18 F-ALF-NOTA-PRGD2	Antiangiogenesis	Gastric carcinoma, non-small cell lung cancer, esophageal cancer, breast cancer, ovarian cancer, cervical cancer	Phase 4	27th Dec. 2018–20th Feb. 2018	NCT03384511

Note: Table 5 shows RGD drugs in clinical trials, with all information sourced from https://clinicaltrials.gov/

Zhao et al. (2019) evaluated 68Ga-labeled dimer and trimer cyclic RGD peptides as PET radiotracers; these have a similar αvβ3 binding affinity to RGD trimers, and the biodistribution properties of Ga radiotracers depend on RGD peptides and radiometal chelates. Schnell et al. (2009) demonstrated that 18 F-labeled glycosylated ARG peptide [18 F]Galacto-RGD could be used for glioma imaging. Zhao et al. (2016) reported that 99 m Tc-4P-RGD 3 and 99 m Tc-3P-RGD 2 were radioactive tracers that could be used for tumor imaging as well as noninvasive monitoring of αvβ3 expression. Both preclinical and clinical studies have shown that radiolabeled RGD peptides (e.g., 99 m Tc-3P-RGD 2, 18 F-Alfatide-I, and 18 F-Alfatide-II) could be used as molecular imaging probes for early cancer detection and to monitor tumor angiogenesis (Liu 2015; Yang et al. 2014) investigated the use of RGD radioactive tracer to monitor tumor angiogenesis. A double-ring RGD called cRGD-ACP-K was used as a PET radioactive tracer for tumor imaging (Park et al. 2014).

In conclusion, RGD can be used in conjunction with imaging agents to aid in the early detection and differentiation of tumors. As previously stated, because RGD has a high specific affinity for αvβ3 integrin, which is overexpressed in tumor neovascularization, RGD can be used as

a carrier to transport radiotracer to integrin αvβ3 on tumor cells.

RGD peptides are widely used in a variety of physiological and pathological processes, most notably in tumor diagnosis and treatment and in anticancer drug development (Huang et al. 2019; Koh et al. 2019; Sun et al. 2015; Xiao et al. 2012; Yigit et al. 2013). It has been reported that many cancer cells and tumor vascular surfaces overexpress αvβ3 integrin (Pierschbacher and Ruoslahti 1984). RGD peptides have a high affinity for αvβ3 and can be attracted to tumor angiogenesis regions (Hadad et al. 2020a), which implies that RGD-modified nanodrug delivery systems can be used for tumor imaging and therapy (Dubey et al. 2004; Fu et al. 2016; Weis and Cheresh 2011b). For targeted drug delivery, linear RGD or cyclic RGD are commonly used in conjunction with nanoparticles (Yin et al. 2014).

Other Applications of RGD

RGD is currently used as a tumor diagnosis or tumor targeting marker. It is also used for biomaterial functionalization (Sani et al. 2021), enhancement of retinal tissue development (Hunt et al. 2017) and osteogenesis (Chen et al. 2015), antithrombotic effect (Bardania et al. 2019; Li et al. 2020b; Wu et al. 2020), and promotion of phagocytic activity of microglia (Dashdulam et al. 2020). It can be used to support the growth, recruitment, and migration of endothelial cells in vitro (Blindt et al. 2006). RGD peptides can also promote cell adhesion to matrix, prevent apoptosis, and accelerate tissue regeneration, and are widely used in tissue engineering (Wang et al. 2013).

RGD-alginate scaffolds can be used for neural retina and derivation transplantation (Hunt et al. 2017). The RGD-CS/HA scaffold's osseointegration ability and biomechanical properties are comparable to those of normal bone tissue (Chen et al. 2015). In the early stages of acute kidney injury, EV-RGD hydrogel attenuates the histopathological damage, reduces tubular damage, and promotes cell proliferation (Zhang et al. 2020). Bardania investigated the in vitro cytotoxicity and hemocompatibility of RGD-modified nanoliposomes (RGD-MNL) encapsulated with a highly effective antiplatelet drug (eptifibatide), and revealed that the RGD-MNL preparation had no obvious cytotoxicity to normal cells or erythrocytes and had the potential to protect and enhance the activity of antiplatelet drugs (Bardania et al. 2019; Li et al. 2020b) created a low-molecular-weight peptide based on RGD-hirudin to prevent thrombosis. Wu et al. designed and prepared TTQ-PEG-c (RGD), a novel organic near-infrared second window (NIR-II) probe that targets the glycoprotein IIb/IIIa receptor (GPIIb /IIIa). It has high NIR-II intensity, good stability, activates platelets, and specifically targets thrombus formation in vitro and in vivo, providing a potential tool for noninvasive diagnosis of early thrombus (Wu et al. 2020; Dashdulam et al. 2020) discovered that an OPN peptide (OPNpt7R, VPNGRGD) containing seven amino acids of RGD increased the phagocytosis activity of microglia cells to the same extent as OPNpt20, and that the RGD motif was critical for this function. Qu et al. (2019) fixed RGD on Hydroxybutyl chitosan (HBC) and synthesized HBC-RGD hydrogel, which can promote bone marrow-derived mesenchymal stem cells (BMSCs) adhesion and proliferation on the hydrogel to cure keloid. Blindt et al. (2006) demonstrated that cRGD promoted endothelial cell growth, recruitment, and migration in vitro.

Overall, RGD ligands have great potential, but due to insufficient research, only a few approaches have been developed for treatment.

Safety of RGD

Because of their inherent safety, biocompatibility, and targeting ability, RGD peptides hold a unique position among all active targeting ligands developed to date. Many studies have found no obvious toxicity after RGD treatment. Zhang et al. (2017b) determined the safety of RGD-Flt23k nanoparticle treatment with RGD-functionalized nanoparticles without detecting hematological toxicity or systemic inflammation, indicating that RGD-functionalized nanoparticles have some safety profile. [68Ga]NODAGA-RGD has good tolerance and metabolic stability in the human body, according to Haubner et al. (2016). With a half-life of 12 min, 18 F-RGD-K5 is rapidly cleared by the renal system and is metabolically stable in human blood 90 min after injection (Doss et al. 2012; Zhang et al. 2017a) investigated the safety and clinical diagnostic value of 68Ga-BBN-RGD PET/CT in prostate cancer patients, discovering that the drug was safe and well tolerated in all healthy volunteers and recruited patients, with no adverse events after injection.

In summary, RGD peptides are a potential cancer therapeutic target due to the biocompatibility and targeting properties of RGD peptides. RGD peptides have a certain safety profile, but some adverse reactions still occur during use, so they need to be monitored and studied for a long time in clinical trials.

Conclusions

RGD peptide–modified nanodrug delivery systems are widely used in the field of tumor treatment. RGD peptides have an excellent specific binding ability to v3 integrin. In the field of nanodrug delivery systems for cancer therapy, particularly chemotherapy, RGD-modified liposomes,

polymers, and inorganic nanoparticles have been extensively studied. Many outstanding outcomes have been obtained. However, the design of RGD-targeted nanocarriers still has a lot of room for improvement. RGD liposomes are still in the early stages of development for target-mediated therapy; for example, nonspecific binding to serum and immune system recognition may render RGD-functionalized liposomes ineffective. RGD-modified liposomes have received little attention in clinical trials to date, which may be due to their instability and low drug loading. Furthermore, we believe that the low drug-loading capacity and poor in vivo stability that RGD-modified polymers and inorganic nanoparticles typically exhibit are two major challenges to overcome. Because tumors and patients are heterogeneous, designing RGD-targeted liposomes, polymers, and inorganic nanocarriers that can be targeted to different patients and tumors remains a difficult task. Furthermore, in vitro specificity is not always consistent with in vivo specificity, because the intracellular environment of tissues is very complex.

Regardless of clinical success, current RGD–integrin drug discovery efforts may facilitate future research by providing a new set of well-characterized tools. These studies could result in the successful development of integrin-targeting drugs. As nanocarriers, RGD-modified liposomes, polymers, and inorganic drugs have broad application prospects and high development value. RGD-modified inorganic, polymer, and liposome nanodelivery systems in the field of cancer treatment require more comprehensive and in-depth research in molecular biology, genetic science, pharmacy, and other related disciplines.

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Declarations

Conflict of interest The authors declare no competing interests.

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