Cyclic Arg-Gly-Asp-polyethyleneglycol-single-walled carbon nanotubes

RGD-PEG-SWNTs

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Chemical name:	Cyclic Arg-Gly-Asp-polyethyleneglycol-single-walled carbon nanotubes	
Abbreviated name:	RGD-PEG-SWNTs	
Synonym:	RGD-SWNTs	
Agent catgeory:	Peptide (nanoparticle)	
Target:	Integrin $\alpha_v\beta_3$	
Target category:	Receptor	
Method of detection:	Optical imaging, Raman imaging, photoacoustic imaging	
Source of signal/contrast:	Single-walled carbon nanotubes (SWNTs)	
Activation:	No	
Studies:	• Rodents	No structure is current available in PubChem.

Background

[PubMed]

The $\alpha_v\beta_3$ integrin, also known as the vitronectin receptor, is a heterodimeric transmembrane glycoprotein found on most cells originating from mesenchyme (1). This receptor is often overexpressed in various tumor cells, including osteosarcomas, neuroblastomas, glioblastomas, invasive melanomas, and carcinomas of the lung, breast, prostate, and bladder. Many extracellular matrix proteins such as fibronectin, vitronectin, thrombospondin, fibrinogen, osteopontin, and tenascin are known to be involved in interactions with various subtypes of integrins. These proteins may contain a variety of

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motifs for potential cell binding; however, one of the most frequent cell-recognition motifs includes an amino acid sequence of Arg-Gly-Asp (RGD), called the "universal cell-recognition site" or a "versatile cell recognition signal" (2). The binding potency of the RGD motif leads to the development of small homing peptides, whose high affinity to the $\alpha_v\beta_3$ integrin provides a promising alternative to antibodies in targeting tumors (3). As a result, RGD analogs are widely used in tumor imaging, anti-angiogenesis treatment, and tumor-associated radionucleotides or chemotherapeutic drugs. Some RGD analogs are currently being used in phase II clinical trials (4). These $\alpha_v\beta_3$ integrin–specific probes will help oncologists improve the delineation of tumors and follow up on the progression of anti-angiogenic therapies.

Single-walled carbon nanotubes (SWNTs) are composed of a single graphene sheet rolled into a tubular shape with a diameter of 0.4–2.0 nm and a length of 20–1,000 nm (5). Because of the graphene structure and seeming one-dimensionality, SWNTs exhibit unique thermal, physical, optical, and electrical properties (6). These properties are closely related to two integers (n, m), where n defines the length of the nanotube and m defines the chiral angle of rolling-up. For instance, SWNTs with the difference of n and m (n-m) evenly divisible by 3 belong to semiconductors and can generate a band gap–related fluorescence when suspended in solutions with surfactant micelles (7). The band gap of 1 eV corresponds to the "biological window" (700–1,300 nm) in fluorescence, where absorption, scattering, and autofluorescence by tissues, blood, and water are at a minimum (8). These optical properties make SWNTs appealing as a contrast agent for near-infrared (NIR) bioluminescence imaging and as an optical absorption agent (8) for photoacoustic imaging (9). In photoacoustic imaging, short pulses of stimulating radiation are absorbed by chromophores in tissues, resulting a subsequent thermal expansion and ultrasonic emission that can be detected by highly sensitive piezoelectric devices (10). Photoacoustic imaging as an emerging modality combines the high optical absorption contrast with diffraction-limited resolution of ultrasonic imaging. In addition, the inherent structure of graphene makes SWNTs an excellent contrast agent for Raman imaging (11). The tangential vibrations in the nanotubes generate diameter-selective resonance Raman scattering that is characterized by a major Raman peak located at the G-band (~1,590 cm^{-1}). SWNTs prepared by various methodologies are hydrophobic. The SWNT surface can be modified with surfactants to increase solubility in aqueous solutions or functionalized with bioactive ligands to target specific sites in tissues (12). Cyclic RGD-polyethyleneglycol-SWNTs (RGD-PEG-SWNTs) are functionalized SWNTs used for Raman imaging (11) or photoacoustic imaging (9) of $\alpha_v\beta_3$ integrin.

Synthesis

[PubMed]

Liu et al. briefly described the synthesis of RGD-SWNTs (13). Initially, SWNTs were prepared with the use of raw gas-phase decomposition of high-pressure carbon monoxide (HiPCO). The obtained SWNTs were sonicated in an aqueous solution of 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-(amine(polyethyleneglycol)$_{2000}$) (DSPE-PEG$_{2000}$-

NH_2) or 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-(amine(polyethyleneglycol)$_{5400}$) (DSPE-PEG$_{5400}$-NH_2) for 1 h followed by centrifugation at 24,000 g for 6 h to functionalize SWNTs. The produced SWNT-PEG-NH_2 was further conjugated with sulphosuccinimidyl 4-N-maleimidomethyl cyclohexane-1-carboxylateat (sulpho-SMCC) (pH 7.2) for 2 h then reacted with thiolated RGD (pH 7.4) overnight, yielding RGD-PEG$_{2000}$-SWNTs or RGD-PEG$_{5400}$-SWNTs.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

Liu et al. used *ex vivo* biodistribution and *in vivo* positron emission tomography (PET) to examine the biodistribution of RGD-PEG$_{5400}$-SWNTs *via* ^{64}Cu labeling (13). In both studies, nude mice bearing U87MG tumors received injections of ~200–300 mCi ^{64}Cu-labeled RGD-PEG$_{5400}$-SWNTs. For the *ex vivo* measurement of biodistribution, the mice were euthanized 24 h post-injection (p.i.), and the tissues were harvested for γ-counting. The tumor uptake increased rapidly, reached a plateau at 6 h p.i., and leveled off in the next 20 h. The measured radioactivity in tumors was 10–15% injected dose (ID)/g for RGD-PEG$_{5400}$-SWNTs, compared to the 3–4% for PEG$_{5400}$-SWNTs. The uptake in other tissues was found to be ~20% ID/g in liver, ~8% ID/g in kidney, and <2% ID/g in blood. As a control, 15 mg/kg c(RGDyK) was co-administrated as a block agent with ^{64}Cu-labeled RGD-PEG$_{5400}$-SWNTs, which significantly reduced the tumor uptake of RGD-PEG$_{5400}$-SWNTs. In addition, mice bearing integrin $\alpha_v\beta_3$–negative tumors (HT-29) were injected with ^{64}Cu-labeled RGD-PEG$_{5400}$-SWNTs. No apparent tumor uptake was found. Liu et al. also examined the biodistribution of RGD-PEG$_{2000}$-SWNTs using the same approach (13). Compared to ^{64}Cu-labeled RGD-PEG$_{5400}$-SWNTs, RGD-PEG$_{2000}$-SWNTs exhibited a lower uptake in U86MG tumors (~5% ID/g) and a higher uptake in the liver (~30% ID/g). To confirm the results, mice bearing U87MG tumors were injected with a high dose of RGD-PEG$_{5400}$-SWNTs (0.5 mg/kg) and euthanized 8 h p.i. The tumoral and liver tissues were excised for Raman spectroscopic measurement. A high intensity at the G-band (~1,580 cm^{-1}) was found in these tissues, validating the presence of SWNTs. These results demonstrated that the uptake occurred *via* the reticuloendothelial system (RES), very similar to uptake of nanoparticles 10–100 nm in diameter.

Keren et al. used RGD-PEG-SWNTs to obtain *in vivo* Raman imaging (11). Mice bearing U87MG tumors were injected intravenously with a 200-μl solution containing 60 pmol RGD-PEG-SWNTs. Raman images were collected 24 h p.i. at 1,593 cm^{-1}. A strong Raman

signal was found in the tumoral area. As a control, mice bearing U87MG tumors were intravenously injected with PEG-SWNTs and examined at the same imaging conditions. No apparent accumulation was found in the tumor area. De la Zerda et al. used RGD-PEG-SWNTs to obtain *in vivo* photoacoustic imaging (9). Mice (n = 4) bearing U87MG tumors (~100 mm^3) were injected intravenously with a 200-µl solution at a concentration of 1.2 µM RGD-PEG-SWNTs. Three-dimensional ultrasound and photoacoustic images were collected for the tumors and their surrounding tissues before injection and up to 4 h p.i. A consistent increase in the photoacoustic signal of the tumor was observed. In comparison, the signal increase as a result of PEG-SWNTs was transient. The accumulation of RGD-PEG-SWNTs in the tumors was found three to five times higher than that of PEG-SWNTs, yielding an approximately eight-fold increase in photoacoustic signal.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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