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Review

Peptides in cancer nanomedicine: Drug carriers, targeting ligands and protease substrates

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ABSTRACT

Peptides are attracting increasing attention as therapeutic agents, as the technologies for peptide development and manufacture continue to mature. Concurrently, with booming research in nanotechnology for biomedical applications, peptides have been studied as an important class of components in nanomedicine, and they have been used either alone or in combination with nanomaterials of every reported composition. Peptides possess many advantages, such as smallness, ease of synthesis and modification, and good biocompatibility. Their functions in cancer nanomedicine, discussed in this review, include serving as drug carriers, as targeting ligands, and as protease-responsive substrates for drug delivery.

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1. Introduction

Traditionally, peptides have been mostly used in polyvalent vaccines [1] or peptide hormones directed against G-protein coupled receptors (GPCRs) [2], because they have lower affinity and faster clearance compared to antibodies and protein ligands. Developments in targeted cytotoxic drugs (radiotherapeutics and toxins) and imaging probes are in large part responsible for the recently revived interest in peptides [3,4]. About 60 peptide drugs had combined sales worldwide approaching $13 billion in 2010 [5]. In addition, about 140 peptide drug candidates are in clinical development. About 17 new peptide molecules enter clinical studies every year now, compared to only about 10 during the 1990s and about 5 in the 1980s [5]. Approved peptide drugs and those in development cover many therapeutic areas, such as oncology, metabolic disorders, and cardiovascular disease.

Although monoclonal antibodies (mAbs) and other large protein ligands have been used clinically as therapeutics and studied for targeted delivery [6–8], two major limitations still exist: poor delivery to tumors—due to their large size, which restricts passive diffusion across endothelial cell membranes in capillaries; and dose-limiting toxicity to the liver and bone marrow—due to nonspecific uptake by the liver and the reticuloendothelial system (RES) [9,10]. The successful use of larger macromolecules, such as mAbs, has therefore been restricted to either vascular targets present on the luminal side of tumor vessel endothelium [8] or hematological malignancies [11]. The advantage of the smaller size of peptides in penetrating tumor has been clearly demonstrated recently [12], where an antibody-mimicking peptide (~3 kDa) showed much greater capacity to target and penetrate tumors than its

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parent antibody despite having a binding affinity that was only 1–10% of the parent antibody. As a targeted therapy and diagnostics delivery vehicle, the rapid renal clearance of peptides could be the additional advantage since they have potentially lower toxicity to bone marrow and liver.

Although peptides possess well-known advantages as drugs, such as specificity, potency, and low toxicity, they have also suffered from practical hurdles such as poor stability, short half-life, and susceptibility to digestion by proteases. However, extensive research may yield peptide drugs that overcome these barriers in the near future. For example, linaclotide, an oral peptide drug developed by Ironwood Pharmaceutics, is in Phase III clinical trials for irritable bowel syndrome. This cysteine-rich, 18-amino acid peptide with three disulfide bridges is stable enough to be taken orally. Moreover, recent advances in phage display technology, combinatorial peptide chemistry, and biology have led to the identification of a richly varied library of bioactive peptide ligands and substrates, and the development of robust strategies for the design and synthesis of peptides as drugs and biological tools [13–15]. In addition, advances in peptide manufacturing have reduced the cost of manufacturing peptides and have enabled small companies to participate in the development of peptide pharmaceuticals.

In the last few decades, nanoparticles have shown great promise in overcoming the delivery barriers of many traditional pharmaceuticals and, as emerging drug delivery platforms, have been brought into clinics. The combination of peptides and nanoparticles in nanomedicine should further strengthen the advantages of each technology. This review will describe some of the recent advances in using peptides in cancer nanomedicine and will be in three parts: peptides as drug carriers; peptides as targeting ligands; and peptides as protease-responsive substrates in drug delivery. An overview of the peptides described in the review, including their sequences, characteristics, and references, is listed in Table 1.

2. Peptides as drug carriers

Efficient passage through the cellular plasma membrane remains a major hurdle for some drugs—particularly molecules that are large, ionized or highly bound to plasma protein [63]. In 1994, a promising approach for overcoming the cellular barrier for intracellular drug delivery – cell-penetrating peptides (CPPs or protein transduction domains, PTDs) – was described by Prochiantz et al. [64]. The first CPP, antennapedia peptide (Antp), was derived from the third helix of the Drosophila melanogaster antennapedia transcription factor homeodomain (amino acids 43–58) [64]. Antp and TAT peptide [65] represent CPPs derived from naturally occurring proteins. A second group contains chimeric CPPs such as transportan (TP), which has 12 amino acids derived from the neuropeptide galanin fused with 14 amino acids derived from the wasp venom mastoparan [66]. A third group contains synthetic CPPs, and of these the polyarginines are the most studied [67]. These peptides have been used for intracellular delivery of various cargos with molecular weights significantly greater than their own [68].

Although it remains difficult to establish a general scheme for a CPP uptake mechanism, there is consensus that the contacts between the CPPs and the cell membrane first take place through electrostatic interactions with proteoglycans, and the cellular uptake pathway is driven by several parameters, including: the primary and secondary structure of the CPP, which determine its ability to interact with cell surface and membrane lipid components; the nature and active concentration of the

Table 1
Peptides described in the review: sequence, characteristics, application and reference.

Peptide	Sequence	Characteristics		Reference
Drug carriers			*Cargos*	
MPG	GALFLGFLGAAGSTMGAWSQPKKKRKV	Amphiphilic, a lysine-rich domain derived from the nuclear localization sequence (NLS)	DNA and siRNA	[16–27]
Pep-1	KETWWETWWTEWSQPKKKRKV	Same hydrophilic domain as MPG, cargo size and nature independent	Peptide and protein	[28–31]
Pep-2	KETWFETWFTEWSQPKKKRKV	Increased complex stability and potency	PNA	[32]
Pep-3	Ac-KWFETWFTEWPKKRK-Cya	Improved cellular uptake	PNA	[33]
CADY	Ac-GLWRALWRLLRSLWRLLWRA-Cya	Secondary amphiphilic peptide	siRNA	[34]
Rath	TPWWRLWTKWHHKRRDLPRKPE	Amphiphilic, β structure dominant	Plasmid, oligonucleotide, antibody and protein	[35]
Penetratin	RQIKIWFQNRRMKWKK	Improved retention and even distribution of single-chain Fvs	Antibody	[36]
VP22	Herpes Simplex Virus Type 1 (HSV-1) structural protein	DNA vaccination	DNA	[37–39]
Targeting ligands			*Target*	
SP5-52	SVSVGMKPSPRP	Conjugated to DSPE-PEG liposomes	Tumor neovasculature	[40]
PIVO-8	SNPFSKPYGLTV	Conjugated to DSPE-PEG liposomes	Tumor angiogenesis	[41]
PIVO-24	YPHYSLPGSSTL			
LyP-1	CGNKRTRGC	Tumor targeting and cytotoxicity	Tumor hypoxia and tumor-induced lymphangiogenesis	[42–46]
RVG	YTIWMPENPRPGTPCDIFTNSRGKRASNG	Synthetic chimeric peptide with RVG and oligoarginine residues	Acetylcholine receptor expressed by neuronal cells	[47]
Activatable probes			*Protease*	
	AA	Acetylated dipeptide conjugated to DOPE	Elastase or proteinase K	[47,48]
	CGLDD	Local delivery of chemotherapeutic agents	MMP-2 and -9	[49]
	PVGLIG	Dextran-PVGLIG-methotrexate conjugate	MMP-2 and -9	[50–52]
	GPLGIAGQ	Conjugated to DOPE for active targeting	MMP-2	[53]
	GKGPLGVRGC	Fe_3O_4 nanoparticles self-assembly gated by logical proteolytic triggers	MMP-2	[54,55]
	GKGVPLSLTMGC		MMP-7	
	SGRSANA	uPA-responsive peptide hydrogel	uPA	[56–58]
	GSGRSAGK	Protease-triggerable, caged liposomes	uPA	[59]
	RVRRSK	Controlled release of encapsulated protein	Furin	[60]
	PLGLAG	Dendrimeric nanoparticles for tumor imaging	MMP-2 and -9	[61]
	GPLGVRGKGG	PEGylated peptide for real-time *in vivo* MMP imaging	MMP-13 (best)	[62]