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Review Article

PEPTIDE NANOMEDICINE IN CANCER TREATMENT

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ABSTRACT

Peptides are those agent which act as a attracting increasing attention as therapeutic agents, as the technologies for peptide development and manufacture continue to mature. Peptides have been studied as one of the important class of components in nanomedicine, and they have been used either alone or in combination with nanomaterials of every reported composition. Peptides provide: A rich repertoire of biologically specific interactions to draw upon; environmentally responsive phase behaviors, which may be tuned to respond to signatures of disease; Opportunities to direct self-assembly; Control over routes of biodegradation. Functions of peptide in cancer nanomedicine include serving as drug carriers; as targeting ligands; and as protease-responsive substrates for drug delivery. Targeted use of nanoparticles *in vitro*, in cells, and *in vivo* requires nanoparticle surface functionalization. Most nanoparticles provide multiple binding sites for different cargo and targeting peptides which can be used for the development of novel approaches for cancer targeting, diagnostics, and therapy. Here main focus is on peptides which have been used for the preparation of different nanoparticles designed for cancer research.

Keywords: Nanomedicine, Peptides, Cancer, Nanotechnology, Drug Carrier, Targeting Ligands, etc.

INTRODUCTION

Nanomedicine, an offshoot of nanotechnology, refers to highly specific, molecular-scale medical intervention for treating disease or repairing damaged tissues.[16] Most broadly, nanomedicine is the process of diagnosing, treating, and preventing disease and traumatic injury, relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body.[17] In short, nanomedicine is the application of nanotechnology to medicine. In April 2006, the journal Nature Materials estimated that 130 nanotech-based drugs and delivery systems were being developed worldwide.[18]Peptides have been mostly used in polyvalent vaccines or peptide hormones directed against G-protein coupled receptors (GPCRs), because they have lower affinity and faster clearance compared to antibodies and protein ligands. The successful use of larger macromolecules, such asmAbs, has therefore been restricted to either vascular targets present on the luminal side of tumor vessel endothelium or hematological malignancies.[1,13] 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.[1,13] Cell type and tissue differences lie at the core of any biomedical research or therapeutic approach. Innate differences between cancer and healthy cells are at the crux of any cancer therapy or diagnostic approach. More recently, antibodies have been used to target nanoparticles to specific cancer types. For example, an antibody against epidermal growth factor receptor (EGFR), cetuximab, has been used to target gold nanoparticles into pancreatic cancer cell Lines with variable EGFR expression, both *in vitro* and in xenograft mouse models.[4].. This review will describe some of the recent advances in using peptides in cancer nanomedicine and will be in three-four parts: peptides as drug carriers; peptides as targeting ligands; and peptides as protease-responsive substrates in drug delivery.[1,13,].Peptides used for delivery of different materials into cells has a relatively recent history. TAT peptide was the first such molecules, which was derived from the *trans*-activating transcriptional activator of human immunodeficiency virus 1. Due to its ability to enter cells, this type of peptide was named cell penetrating peptide' (CPP). Although many more 'advanced' CPP peptides have been developed subsequently, TAT is still in use and provides a reliable vehicle for delivery of different cargo into cells. [15]Peptides can be considered to be 'pre-designed' as they were developed to target specific antigen epitopes, as an alternative to antibodies [15].and peptide drug delivery in cancer, an overview of the peptides described in the review, including their sequences, characteristics, applications and references is listed in table 1.[1]

Table 1:showing peptide sequence, characteristic and their cargos[1]

PEPTIDE	SEQUENCE	CHARACTERISTICS	CARGOS
Drug carriers	GALFLGFLGAAGSTMGAW	Amphiphilic, a lysine-rich domain derived from the nuclear	DNA and siRNAs
MPG	SQPKKKRKV	localization sequence (NLS)	
Pep-1	KETWWETWWTEWSQPK KKRKV	Same hydrophilic domain as MPG, cargo size and nature independent	Peptide and protein
Pep-2	KETWFETWFTEWSQPKK KRKV	Increased complex stability and potency	PNA
Penetrating	RQIKIWFQNRRMKWKK	Improved retention and even distribution of single-chain Fvs	Antibody
Targeting ligands			**Target**
SP5-52	SVSVGMKPSPRP	Conjugated to DSPE-PEG liposome's	Tumor neovasculature
PIVO-8	SNPFSKPYGLTV	Conjugated to DSPE-PEG liposome's	tumor angiogenesis
PIVO-24	YPHYSLPGSSTL		
LyP-1	CGNKRTRGC	Tumor targeting and cytotoxicity	Tumor hypoxia and tumor-inducedlymph angiogenesis
PEPTIDE	**SEQUENCE**	**CHARACTERISTICS**	**Target**

RVG	YTIWMPENPRPGTPCDIF TNSRGKRASNG	Synthetic chimeric peptide with RVG and oligoarginine residues	Acetylcholine receptor expressedby neuronal cells
Activatable probes			**Protease**
	AA	Acetylated dipeptide conjugated to DOPE	Elastase or proteinase K
	CGLDD	Local delivery of chemotherapeutic agents	MMP-2 and -9
	PVGLIG	Dextran-PVGLIG-methotrexate conjugate	MMP-2 and -9
	GPLGIAGQ	Conjugated to DOPE for active targeting	MMP-2
GKGPLGVRGC		Fe3O4 nanoparticles self-assembly gated by logical proteolytic triggers.	MMP-2

Tumor (cancer)

Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells. Cancer cells manifest, to varying degrees, four characteristics that distinguish them from normal cells. These are1) Uncontrolled proliferation 2) Dedifferentiation and loss of function 3) Invasiveness 4) Metastasis.

Main Causes of cancer-A normal cell turns into a cancer cell because of a mutation in its DNA, which can be inherited or acquired. It begins with an alteration to the structure of DNA that is found in all human cells. DNA provides instruction to cells, like when to grow and reproduce. Mutation in DNA changes these instructions, so the cells carry on growing. Cancer affects two specific genes known as: a) Oncogen (Activation of proto-Oncogen to Oncogen) b) Tumor suppressor gene (Inactivation).Combination of these two can spread cancer quickly usually via lymphatic system [22, 23]. See Fig.1 [21, 22]for Formation of cancer (tumor) .Nanotechnology has the power to radically change the way cancer is diagnosed, imaged and treated. Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can transit out of blood vessels. Nanodevices can provide rapid and sensitive detection of cancer-related molecules by enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. This makes cancer screening faster and more cost-efficient, shown in figure 2.See Fig.2 [18] For Improved diagnostic. The major areas in which nanomedicine is being developed in cancer include: Prevention and control. Developing nanoscale devices to deliver cancer prevention agents and designing multicomponent anticancer vaccines. Early detection and proteomics. Developing "smart" collection platforms for simultaneous mass analysis of cancer-associated markers. [22, 23].

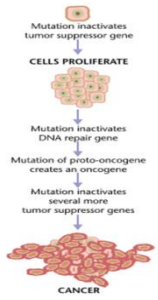

Figure1:formation of cancer

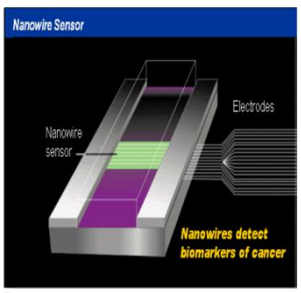

Figure 2: Improved Diagnostics

Peptide used as a nanomedicine in cancer as

Use of Peptides as drug carriers in cancer

Cellular plasma membrane having major importance for some drugs particularly molecules that are large, ionized or highly bound to plasma protein [2] .In the year of 1994, cell penetrating peptides (CPPs or protein transduction domains, (PTDs) was described by Prochiantz et al. [3] The first CPP, antennapedia peptide (Antp), was from the third helix of the Drosophilamelanogaster antennapedia

transcription factor homeodomain (amino acids 43–58). TAT & Antp peptide shows CPPs derived from naturally occurring proteins.[4] A second group contains chimeric CPPs[5] A third group contains synthetic CPPs.[6]It is difficult to establish uptake of CPP ;with the help of electrostatic interaction along with proteoglycans there is contacts between Cell membrane & CPPs. Cellular uptake pathway is determined 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 cargo; the cell type and membrane composition; and experimental conditions such as salt and CPP concentrations. There are two main strategies in CPP-mediated drug delivery: the first requires covalent linkage with the cargo and the second involves formation of stable, non-covalent complexes.

The method having advantages for in vivo applications, like rationalization, reproducibility of the procedure, and control of the stoichiometry of the CPP–cargo & limitation is altering the biological activity of the cargo. For instance, coupling siRNAs to CPP often led to restricted biological activity so non-covalent strategies come out more appropriate. [7]It based on amphiphilic peptide having hydrophilic (polar) domain and a hydrophobic (non-polar) domain. The hydrophilic domain is required for complexation with hydrophilic negatively charged molecules, to target an intracellular compartment, and to improve the solubility of the vector. The hydrophobic domain is required for membrane anchoring and for complexation with hydrophobic cargos. The amphiphilic character of such peptides may arise from either their primary structure or secondary structure (Fig. 3) [1]. Complexation between CPPs and cargo molecules through electrostatic/hydrophobic interactions is shown in Fig.4 [1].α-helical structure is secondary amphiphilic peptides used as drug carriers. Several peptides able to condense DNA associated with peptides that favor endosomal escape, including fusion peptide of HA2 subunit of influenza hemaglutinin have been described. Synthetic peptide analogs such as GALA (WEAALAEALAEALAEHLAEALAEALEALAA) KALA(WEAKLAKALAKALAKHLAKALAKALKACEA),JTS1(GLFEALLELLESLWELLLEA),ppTG1(GLFKALLKLLKSLWKLLLKA),MPG(GALFLGFLGAAGSTMGAWSQPKKKRKV) and histidine rich peptides have also been reported as potent gene delivery systems MPG (GALFLGFLGAAGSTMGAWSQPKKKRKV) is a primary amphiphilic peptide consisting of three domains.

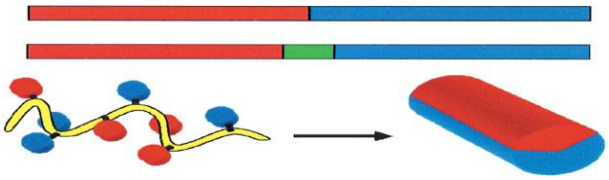

Figure 3: Schematic representation of amphiphilic peptides.

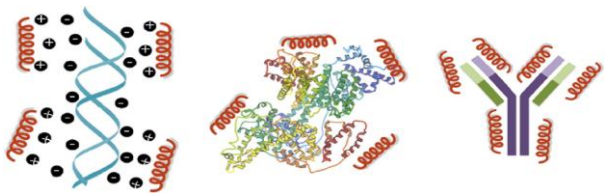

Figure 4:Non Covalent Complexation between CPPs and Cargos

An MPG variant possessing a single mutation in the NLS (MPG 186 ΔNLS) could also deliver siRNAs into cultured cells with high efficiency (~90% cells). While MPG-transfected fluores cently

labeled siRNAs localized rapidly into the nucleus, it remained essentially in the cytoplasm when transfected with MPG 189 ΔNLS,

where it was more efficient in its silencing function than in the nucleus; Pep-1 (KETWWETWWTEWSQPKKKRKV) is also a primary amphiphilic peptide consisting of three domains. Its lysine-rich hydrophilic domains (KKKRKV) are the same as those of MPG, but it differs in its hydrophobic domains. The hydrophobic motif of Pep-1 corresponds to a tryptophan-rich cluster (KETWWETWWTEW), which is required for efficient targeting to the cell membrane and for hydrophobic interactions with proteins. The Pep-1 strategy has also been applied to delivery of proteins and peptides in vivo in different animal models, via intravenous, intratracheal, and intratumoral injections, transduction into oocytes and topical application. . Pep-2 (KETWFETWFTEWSQPKKKRKV) differs from Pep-1 essentially by two Phe residues at positions 5 and 9, which replace Trp residues in the hydrophobic domain Pep-1 carrier promotes the cellular uptake of small peptides and large proteins, independently of their nature and size, into a large panel of cell types Intratumoral injection of Pep-3/HypNA-pPNA in PC-3 xenografted mice was shown to potently inhibited tumor growth in a concentration-dependent manner, with more than 92% for 5 µg of antisense HypNA-pPNA. For Non-covalent complexation between CPPs and cargo see Fig.4. Cargo-specific CPP design will be essential to the development of safe and effective therapeutics. For cancer applications, tumor cell targeting (passive, active or both) should result in improved drug efficiency, reduced side effects (a major burden for patients in current systemic cancer treatment), and increased therapeutic window. This could lead to the ability to target specific cell and tissue types and to control the fate of cargoes inside cells. Characterization of the structure-activity relationship of individual CPPs will allow tailoring of specific CPPs to particular intracellular targets and optimization of potency.

Use of Peptides as targeting ligands in cancer

In 1958, the first attempt to deliver a ligands-directed drug to leukemic cells was published by Matte et al. [8] Proteins and peptides, carbohydrates, vitamins, antibodies, and aptamer are the common ligands used to increase the specificity of targeting systems. Among them peptides is most important because it having advantages like : can achieve high specificity, they are smaller than antibodies, can be synthesized by chemical methods at a large scale, Most traditional drug delivery methods (except for time-release formulations) release drugs instantaneously, and it can result in peak concentrations that are toxic to tissues, The main strategy to select proper peptide ligands is to screen peptide libraries produced by either phage display or chemical synthesis,[9,10] Phage display can be used to identify peptides that target a specific receptor, Moreover, phage display is adaptable to both in vitro and in vivo studies; many peptide ligands have been developed for various types of cells & or receptors , such as integrin receptors, thrombin receptors tumor cells, cardiomyocytes, and pancreatic β cells. Tumor-targeting peptides have been successfully incorporated in vehicles that deliver targeted imaging agents, small molecule drugs, oligonucleotides, liposomes, and inorganic nanoparticles to tumors. Therapeutic nanoparticles are shown in Fig .5

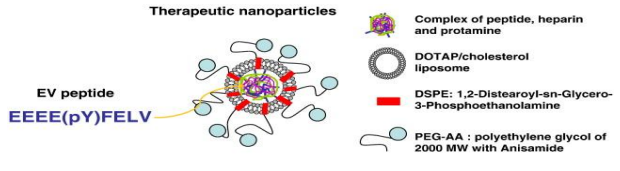

Figure 5:Therapeutic Nanoparticles

Peptide-related nanoparticles, such as peptide aptamer and peptidomimetic self-assembled nanoparticles also have shown great potential in targeted drug delivery. The former are more frequently used directly as drugs interfering with the function of receptors, while the later have more expanded applications in tumor imaging, tumor targeting delivery and vaccination. [11]The use of these peptides has increased the specificity and efficacy of drug delivery while reducing side effects. Wu et al. report that the peptide SP5-52 (sequence: SVSVGMKP 416 SPRP), identified by in vivo phage display, conjugated specifically to PEGylated distearoyl phosphatidyl ethanolamine (DSPE-PEG) liposome's targeted tumor blood vessels. After the peptide was conjugated onto PEG-DSPE liposome's containing doxorubicin, it was shown to inhibit the angiogenesis of tumors, resulting in increased therapeutic efficacy and higher survival rates of both human lung and oral cancer xenograft mice.SP5-52 recognized tumor neovasculature but not normal blood vessels in xenograft mice models. Targeting phage was shown to home to tumor tissues from eight different types of human tumor xenograft following in vivo phage display experiments; tumor tissues from these eight different cancer cell lines contained >8-fold more SP5-52 than normal organs. Using LyP-1 as the targeting ligands, Sailor et al. presented a cooperative nanosystem consisting of two discrete nanomaterials. The first was gold nanorod (NR) "activators" that populated the porous vessels of tumors and acted as photo thermal antennas to facilitate tumor heating via remote near-infrared laser irradiation. The second component was: targeted nanoparticles consisting of either magnetic nanoworms (NW) or doxorubicin loaded liposome's (LP). Tumor-induced lymph node (LN) lymph angiogenesis usually precedes metastasis and leads to increased tumor spread to distal LNs; it has been shown to be the presence of non-sentinel LN metastases in animal tumor models and human breast cancer and melanoma. Between day 7 and day 21 after inoculation with 4 T1 cells, the size of tumor-draining LNs did not change; the fluorescent intensity from the injected probe kept increasing, indicating that the lymphatic vessel density increased with time. Moreover, even 24 hr after Cy5.5 -LyP-1 injection, 5 much stronger fluorescent signals could be measured inside tumor draining LNs than after injection of non-conjugated Cy5.5, confirming specific binding of this peptide probe to lymphatic vessels. The results demonstrated that Cy5.5-LyP-1 facilitated visualization of the expansion of lymphatic networks within the tumor draining sentinel LNs, even before tumor metastasis occurred. To enable siRNAs binding, a chimeric peptide was synthesized by adding nonamer arginine residues at the carboxy terminus of RVG to create RVG-9R.When GFP siRNAs were complexed with the positively charge RVG-9R peptide and injected intravenously into GFP transgenic mice for three consecutive days, GFP expression was significantly decreased in the brain but not in the liver or spleen, confirming the specificity of brain targeting. Similar results were obtained when siRNAs against SOD1 was used; siRNAs was only detected in the brain but not in the spleen or liver after treatment this brain cell targeting peptide that penetrates the blood–brain barrier has since been incorporated into liposomes and exosomes. The targeting peptides are often fused with other functional peptides, such as CPPs, or attached to nanoparticles to facilitate drug delivery. Peptide targeting itself is becoming combinatorial with the use of more than one peptide in a single entity, the use of peptides that also serve as Proteolytic substrates to provide more function etc. These discoveries and the experience gained could yield completely novel approaches to cancer treatment by nanomedicine.

Peptides in responsive drug delivery systems (cancer)

Proteases (or proteinase) about 2% of the human genome, and play role in regulatory pathways & makes them useful as prognostic indicators. Proteolysis is a simple hydrolytic cleavage of the amide bond between two adjacent amino acid residues catalyzed by proteases. Without the catalytic assistance of protease, protein hydrolysis would be a very slow process. Some proteases are expressed as proenzymes, while others are complexed with natural enzyme-inhibitors. Using various mechanisms Proteolytic activity is regulated. For example, intracellular proteolysis is regulated by segregation within organelles such as lysosomes. Their enzymatic properties can be restored only when needed. Proteases are catalytic enzymes; one protease molecule could specifically activate hundreds, or even thousands of its substrates. Cancer-associated proteases (CAPs) have gained attraction recently as a new method of tumor targeting. CAPs are a set of proteases that are usually absent for tumor at very low concentrations in healthy tissues but are often highly up-regulated in cancerous tissues. See Fig.6 for Brain-specific gene silencing after i.v. injection of siRNAs/RVG-9R complex. Some

of extensively studied CAPs include urokinase plasminogen activator (uPA), many of the matrix metalloproteases (MMP), and some of the catharsis.

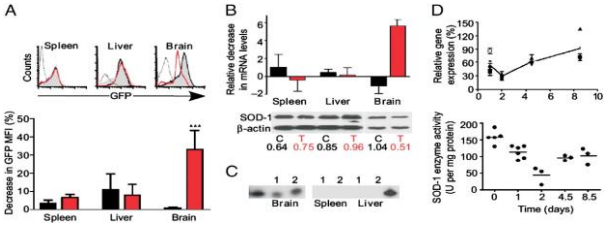

Figure 6:Brain-specific gene silencing after i.v. injection of siRNAs/RVG-9R complex

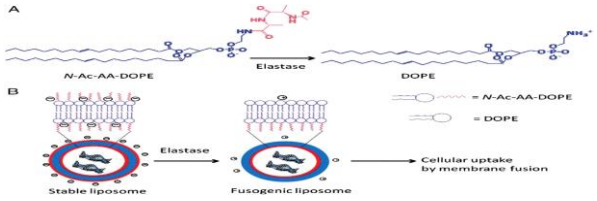

Figure7:Removal of N-Ac-AA by elastase results in charge reversal

Earliest examples, of protease-Activatable liposome's were designed by conjugating an acetylated dipeptide substrate (N-Ac-AA) through its carboxyl terminus to the amino group of 1, 2-dioleoyl sn-glycero-3-phosphoethanolamine (DOPE) to promote cellular internalization. The resulting peptide–lipid (N-Ac-AA-DOPE), together with dioleoyl trimethyl ammonium propane (DOTAP) and phosphatidyl ethanolamine (PE), was assembled into non-fusogenic liposomes. MMPs, probably the most studied CAPs for tumor-responsive drug delivery, are a family of at least 24 zinc-dependent endoprotease. They can degrade most components of the extracellular matrix and basement membrane. Extensive studies have shown frequent over expression of several MMPs in many forms of human tumor. The liposomes were activated by elastase or proteinase K to become fusogenic for enhanced intracellular delivery (Fig.6)[1] These studies demonstrated a clear relationship between increased MMP expression and poor clinical outcome in a number of cancers including breast (MMP-11), colon (MMP-1), gastric (MMP-2 and MMP-9), non-small cell lung cancer (MMP-13), esophageal (MMP-7), and small-cell lung cancer (MMP-3, MMP-11 and MMP-14).Therefore, MMPs are attractive targets for protease-sensitive drug delivery.Figure7 shows Removal of N-Ac-AA by elastase results in charge reversal, thus enhancing its ability to fuse with the plasma membrane for drug delivery. The catalytic function could amplify signal outputs and improves detection limits significantly for disease detection and diagnosis. In addition to improving tumor-selective delivery of cancer therapeutics or imaging probes, these protease-sensitive nanoparticles could function to reduce their undesired activity/signal in normal tissues, including liver, heart and bone marrow. Since disease-associated protease activities vary by individual and by stage of disease, greater understanding is required of targeting protease structures, mechanisms, distribution, and regulation in vivo. The advantages and promise shown by protease-responsive nanoparticles, some issues remain for future development and realization in clinical use. Finally, as with any other nanoparticles or nano-assemblies, the properties of the whole particles will largely determine their in vivo fates and performance and, thus, should be carefully designed and characterized.[1, 12]

Nanoparticle Carrying Peptide as a Therapeutics agent

Cell killing peptides can sometimes be self-assembled into biodegradable nanoparticles or attached to nonpeptide scaffolding.

For example, a cationic alphahelical peptide based on the sequence KLAKLAK is universally cytotoxic causing membrane disruption. Recently, a (KLAKLAK) 2 peptide was integrated into a peptide amphiphiles that self-assembles into cylindrical nanofibers. Although in this circumstance these biodegradable nanoparticles were used to treat cultured breast cancer cells, it is anticipated that cytotoxic peptide(s) modified in this way may provide a safe agent for *in vivo* anticancer treatment. Another universally cytotoxic peptide is melittin, a portion of the larger peptide contained in bee venom. This 26 amino acid *α*-helical peptide (GIGAVLKVLT TGLPALISWI KRKRQQ) causes cell death through cytolysis. Use of these nanoconstructs lead to a reduction of tumor volume in syngeneic B16F10 mouse melanoma tumors and human melanoma cells in culture. Tubulysins cause depolymerization of cell microtubules, which prevents completion of mycosis and leads to apoptosis of proliferating cells. With HT29 human colon or H460 non-small cell lung carcinoma. In mice, tumor growth delay matched that which could be achieved by paclitaxel but without adverse effects such as loss of body weight.[14]

Mechanisms of peptide-mediated tumor targeting

Environmentally responsive delivery systems make use of tumor pathology to trigger release of therapeutic agents at the target site. The list of potential biomarkers is extensive; the list of potential biomarkers provided by the tumor microenvironment can be broadly classified into physical or molecular triggers. Physical triggers are activated by the nature of the tumor microenvironment. Peptides provide a level of molecular specificity that is naturally suited to the development of environmentally responsive drug carriers.[13,26,27,28] Peptide having secondary and tertiary structures enable a degree of control and functionality that surpasses what is easily achievable using lipids and non-biological polymers. As the development of cancer-targeted nanocarriers continues to expand, peptides are providing these formulations with critical functionalities necessary to target disease.[13]

Nanoparticle (nanomedicine) delivery of a peptide act as a targeting EGFR signaling

EGFR serves as an important therapeutic target because of its over-expression in many cancers. Peptide-based therapy aimed at blocking intracellular protein–protein interactions during EGFR signaling and evaluated a targetable lipid carrier system that can deliver peptides to intracellular targets in human cancer cells. Peptide-based nanoparticles enhance cellular delivery of the hydrophobic anticancer drug ellipticine through caveolae-dependent endocytosis. Peptide (EAK16-II) has been found to stabilize the hydrophobic anticancer agent ellipticine (EPT) in aqueous solution.[29]

Peptide-mediated cancer targeting of nanoconjugates

Targeted use of nanoparticles *in vitro*, in cells, and *in vivo* requires nanoparticle surface functionalization. Moieties that can be used for such a purpose include small molecules as well as polymers made of different biological and organic materials. Short amino acid polymers, peptides, can often rival target binding avidity of much larger molecules. Most nanoparticles provide multiple binding sites for different cargo and targeting peptides which can be used for the development of novel approaches for cancer targeting, diagnostics, and therapy.[14]

Importance of nanotechnology in cancer research

1) Nanotechnology holds tremendous potential for overcoming many of the problems that conventional methods face in the treatment, diagnosis and detection of cancer. 2) In particular, nanoparticles (nanoscale-sized particles) have been developed and investigated for cancer diagnostics and therapeutics; these materials

are hereafter referred to as NP-CDTs.3) In addition, functionalized nanoparticles target specific receptors that are over-expressed on surfaces of cancer cells, and this in turn facilitates the uptake of drug-loaded nanoparticles via endocytic pathways.[30]

Importance of Peptide nanomedicine in cancer treatment

1) 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. 2) Peptides possess many advantages, such as smallness, ease of synthesis and modification, and good biocompatibility the use of

peptides in theragnostic nanomedicine has drawn increasing attention. 3)The characteristics of peptides are especially suitable for imaging, since they can achieve target-specific accumulation and signal amplification, hence high signal-to-background ratios. 4) As the challenges in discovery, development, and manufacturing are being met, combined with continued research, peptide-based nano theragnostic will play an increasingly role in cancer diagnosis and therapeutics.

Limitation

Rapid renal clearance, insufficient disease site targeting and accumulation, undesired cargo release and in vivo instability .No matter the nature of the delivery system, major attention must be paid to the targeting and controlled release of the carrier/cargo into specific tissues and to limit the dispersion in non-targeted areas. (1, 12, 31)

CONCLUSIONS

Peptide targeting of nanoparticle is steadily gaining ascendance in cancer research. Peptides created by phage display or other reiterative random library approaches are tested as targeting agents attached to nanoparticles even as their target epitopes are as yet in the process of discovery. As the number of peptide–nanoconjugates examples increases new ideas on how to use such polyvalent assemblies are being formed. In the past few years, the use of peptides in theragnostic nanomedicine has drawn increasing attention. With the further development of theragnostic nanomedicine, the role of peptides will continue to expand. Depending on the applications, limitations of peptides may include: rapid renal clearance, insufficient disease site targeting and accumulation, undesired cargo release and in vivo instability .No matter the nature of the delivery system, major attention must be paid to the targeting and controlled release of the carrier/cargo into specific tissues and to limit the dispersion in non-targeted areas. In other words, the physicochemical and pharmacochemical properties of nano-complexes as a whole must be carefully designed and characterized to implement their desired functions. As the challenges in discovery, development, and manufacturing are being met, combined with continued research, peptide-based nanotheranostics will play an increasingly role in cancer diagnosis and therapeutics. (1, 12, 14)

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