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Cancer Therapeutics and Delivery Strategies of Bioactive Peptides

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Abstract: ***New therapies are constantly evolving in man's fight aimed towards successful prevention and treatment of cancer. This paper discusses the role of peptides in cancer therapy. Peptides hold great potential in cancer therapy and diagnostics. This is due to the unique advantages of peptides, such as low molecular weight, ability to specifically target tumor cells and low toxicity in normal tissues. The potential of peptides in cancer treatment is evident from a variety of different strategies that are available to address the progression of tumor growth and propagation of the disease. Peptide-based chemotherapy can be mainly divided into three types, peptide-alone therapy, peptide vaccines, and peptide-conjugated nanomaterials. Peptide-alone therapy may specifically enhance the immune system's response to kill tumor cells. Peptide-based vaccines have been used in advanced cancers to improve patient's overall survival. In this review, we mainly focus on the new advances of peptides in cancer therapy, including diagnosis, treatment, prognosis development of anticancer peptides, use of peptides for drug delivery and cancer targeting.***

Keywords: Peptides, Cancer, Peptide Conjugates, Tumor homing peptides, Peptide Targeted cancer therapy

1. Peptides

Peptides are naturally occurring biological molecules. Peptides are found in living organisms and play a key role in all manner of biological activity [1]. Like proteins, peptides are formed (synthesized) naturally from transcription of a sequence of the genetic code, DNA. Transcription is the biological process of copying a specific DNA gene sequence into a messenger molecule, mRNA, which then carries the code for a given peptide or protein. Reading from the mRNA, a chain of ami no acids is joined together by peptide bonds to form a single molecule. Peptides, polypeptides, and proteins are all chains of amino acids linked via peptide bonds. The distinction between these peptides, polypeptides, and proteins is not well defined but is based on length. Peptides are short chains of amino acids whereas polypeptides and proteins are long chains. Peptides are formed by combinations of amino acids linked by peptide bonds through the dehydration condensation reaction [2]. Peptides can be obtained conveniently from the products of proteolysis, direct synthesis by the body, or artificial synthesis.

The peptides are currently being tested as therapeutics is fewer than 40 amino acids in length. Polypeptides can be over 100 amino acids long and proteins are made up of one or more of these polypeptide chains. The properties of a peptide depend on which of the 21 amino acids they are composed of, with the properties of the amino acid side chains affecting their conformation, thus function, and role within the body [3]. **Peptides are of particular interest as therapeutic drugs because the body naturally produces many different peptides, this means they are relatively well-tolerated as therapeutics and have fewer side-effects.** Peptides are most versatile tools with immense potential for the development of cancer diagnostics and therapies.

CANCER Cancer is a highly complex disease to understand because it entails multiple cellular physiological systems such as cell signaling and apoptosis. Cancer is caused by damaging of genes which control growth and division of cell. Cancerous cell need blood supply to grow. A hormone like molecule causes nearby blood vessels to grow towards the cell to supply the oxygen and other nutrients [4].

Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumor mass, vascularization, and metastasis (spread of cancer to other parts of the body). Though angiogenesis (growth of new blood vessels from preexisting vessels) is a normal and vital process in growth and development, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. There is a multitude of ways to utilize them for cancer intervention: mimicry of natural proteins to either enhance or inhibit signaling, targeting therapeutics specifically to cancer cells, or using them as a tool for transbarrier delivery [5]. There are several aspects that make peptides ideal tools for developing new therapies. The advantage is their size which is optimum between full proteins such as antibodies and small molecular bimolecular mimics allows delivery advantage, specific mimicry of bio-logical interactions, ease of synthesis and modification, tumor penetrating ability, and good biocompatibility.

Cancer is one of the leading causes of death worldwide after Cardiovascular Diseases. The American cancer society stated that by 2030 the number of new cancer incidences will rise to 21.7 million and number of cancer death may rise to 13 million. State – of – the – art treatment of cancer today is accomplished by controller of surgical procedures, radiation therapy and chemotherapy. Cancer sensing properties needed to achieve the ultimate goal of targeting cancer treatment using drugs molecules or drug conjugates. The idea is to exploit only biochemical characteristic of the cancer cells which may be different from healthy normal cell in order to achieve selective therapeutic effect against the

malignant cells. Such characteristic may include deregulations of translation regulators, changes in epigenetic regulation mechanisms, over production of enzymes, or changes in the cellular microenvironment such as lower pH [6].

Cancer can be cured by rectifying the damaging mechanism of the genes or by stopping the blood supply to the cells or by destroying it. Detection is possible by confirming the growth of the cells. Cytotoxic drugs are effective at killing cancer cells and are the workhorse of most cancer therapy (along with surgery and radiation), but they work by killing neoplastic cells marginally better than they kill other proliferating cells. Nanotechnology could pave the way in solving one of the most challenging problems in medicine, which is elimination of cancer with minimum harm to normal body tissue [4]. Scientists and researchers hope that nanotechnology can be used to create therapeutic agents that target specific cells and deliver the toxin in a controlled, time-release manner. The aim is to create single agent that detect and treat cancer.

Peptides can be utilized in a number of different ways in treating cancer [7]. This includes using peptides directly as drugs (e. g. angiogenesis inhibitors), tumor targeting agents that carry cytotoxic drugs and radionuclides (targeted chemotherapy and radiation therapy), hormones, and vaccines [8]. Due to the ability to bind to different receptors and also being part of several biochemical pathways, peptides act as potential diagnostic tool and biomarkers in cancer progression. Different possible cancer treatment options using peptides are summarized in Fig: 1

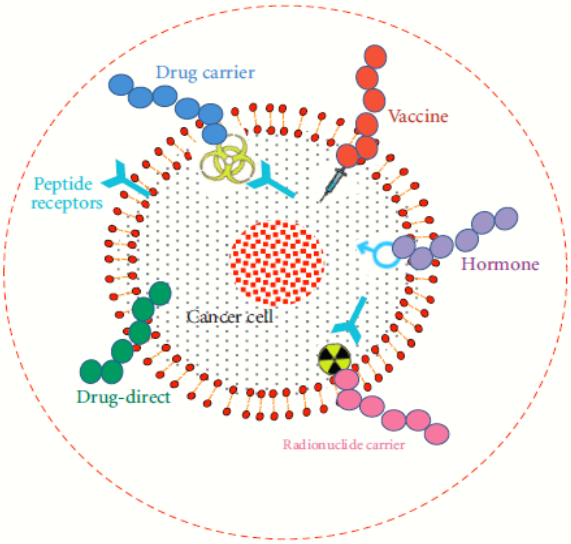

Figure 1: Treatment options of cancer using peptides. Peptides can be used as anticancer drug, cytotoxic drug carrier, vaccine, hormones, and radionuclide carrier.

Conventional Cancer Treatment

One of the treatment options is surgery, which involves removal of the cancerous part. However, the limitation is that one looses the organ and cancer may reappear [4]. The second option is radiation therapy where the cancerous cells are burnt by radiation of specific frequency band and intensity. The third option is chemotherapy where cancerous cells are killed by drugs toxic to cells or by stopping cells from taking nutrients needed to divide or stop the mechanism responsible for cell division.

Peptides for cancer treatment

Peptides used for the treatment of cancer are divided into several functional categories: tumor cell-killing peptides that destroy cells through a variety of mechanisms, tumor cell penetrating peptides that cause transmission through cell membranes, tumor cell-homing peptides that cause targeted transmission to cancer cells, and peptides that intervene in cancer-related protein–protein interactions (PPIs) (Fig.2) [9].

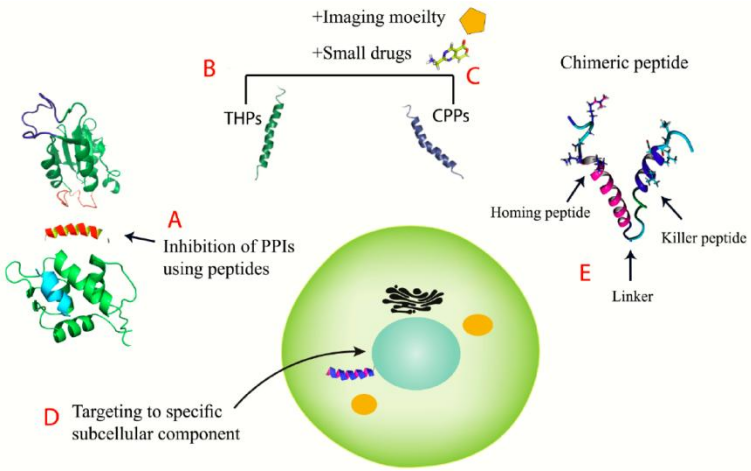

Figure 2: Schematic representation of various applications of peptides for cancer therapy. A) Intervening in cancer-related protein–protein interactions using peptides; B) Tumor cell-homing peptides that cause targeted transmission to cancer cells; C) Tumor cell-penetrating peptides that cause transmission through cell membranes; D) Targeting specific sub cellular compartments using peptides; E) Chimeric peptide that can destroy cancer cells selectively.

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In the new era of personalized or precision medicines, the goal of therapeutic management is to use tumor-and patient-specific genetic and molecular aberrations for the selection of specific targeted therapies for each patients. Inherent to this individual assessment of using genomic and molecular profiling of cancer, appropriate clinical management requires molecular probes that are capable of homing specifically to primary or metastatic tumor mass. The cancer-targeting antibodies exhibit excellent performance as vehicles to deliver the radionuclides for imaging and the cytotoxic agents for chemotherapies. The fragment crystallizable region of the antibody trends to non-specifically bind to the RES, causing notable toxicity towards tissues like liver, spleen, and bone marrow. In addition, thanks to their high relative molecular mass (up to 160 kDa), they're poorly diffused into the tumor mass or don't reach the brain just in case of central nervous system neoplasms, resulting in the need of the transient opening of the Blood-Brain-Barrier (BBB). Therapeutic antibodies are very specific and effective thus are rather difficult and particularly expensive to produce in mass scale. In the light of these shortcomings, targeting peptides can be considered as an alternative vehicle for the delivery of diagnostic agents and/or anti-cancer drugs. Compared to antibodies, targeting peptides enjoy non-immunogenicity, fast blood clearance, better intra tumoral diffusion thanks to their lower relative molecular mass, and excel lent tolerability by patients. The short half-life of the peptides which will in some cases reduce the buildup at the target is usually considered together of their limitations. Prolonged half-life of the peptides are often obtained by preventing the degradation by the blood proteases through i) presence of a cycle that are formed (eg: disulfide bonds between two cysteines), ii) blocking of C-and N-terminal, iii) replacement of eukaryotic amino acids by their D-counterparts or iv) use of the unnatural amino acids incompatible with endogenous proteases [10].

Peptides with different bioactive sequences are often fused with one another to extend potency. They can also act as carriers for targeted-therapy drugs, like those utilized in chemotherapy. Use of unstructured hydrophilic and biodegradable proteins as bulking moieties, e. g., XTEN protein polymers, is another approach for half-life extension and reduction of renal clearance of peptides by increasing the hydrodynamic volume [11]. Bioavailability and stability of peptide drug candidates can be improved by chemical modifications such as peptide sequence modifications or innovative formulation techniques such as the integration of peptides into particles, gels or liposomes. Peptide stability can also be improved by blocking their respective termini through N-terminal acylation and C-terminal amidation. Compared to proteins, antibodies, and small-molecule drugs, peptides have a greater potential for addressing the challenges of cancer treatment. The capability to have an effect on “undruggable” targets and to interfere with proton-protein interaction (PPIs) is an important advantage of peptides compared to small molecules. Due to their unique biological and chemical properties, peptides have higher affinity and specificity to targets. They have lower nonspecific toxicity profiles compared to small molecules.

Anticancer Peptides

Anticancer peptides are a term used to distinguish a group of peptides that are derived from antimicrobial peptides, but show cancer-selective toxicity by membranolytic activity. Many of them have been found from the amphibian skin and they are able to distinguish cancer (or microbial) cells due to abnormalities in cancer cell membrane composition [12]. The mechanism involves the inhibition of angiogenesis, protein-protein interactions, enzymes, proteins, signal transduction pathways, or organic phenomenon. Angiogenesis involves the migration, growth, and the differentiation of endothelial cells, which line within the walls of blood vessel. Angiogenesis requires the binding of signaling molecules, like vascular endothelial protein (VEGF), to receptors on the surface of normal endothelial cells. An example of such is Anginex – a positively charged, amphipathic peptide that forms b-sheet, and was artificially designed based on the sequences of several anti-angiogenic proteins, including platelet factor-4, interleukin-8, and bactericidal permeability-increasing protein – resulting in an efficient antitumor peptides. GRP (Gastrin-releasing peptide) peptides were shown to bind selectively to the G-protein-coupled receptors on the cell surface, stimulating the growth of various malignancies in murine and human cancer models [13]. Thus, it's been proposed that the secretion of GRP by neuroendocrine cells could be liable for the event and progression of prostatic adenocarcinoma to androgen independence. GRP is cosmopolitan in lung and gastrointestinal tracts. It is produced in Small Cell Lung Cancer (SCLC), breast, prostatic, and pancreatic cancer and functions as a growth factor [14].

Poor penetration of anticancer drugs into tumors can be an important factor limiting their efficacy. In solid tumors, many anticancer drugs penetrate only 3 to 5 cell diameters from the blood vessels, leading to reduced efficacy and the development of drug resistance identified a tumor-penetrating peptide, iRGD, that, when chemically conjugated to a drug, can carry the drug deep into extra vascular tumor tissue [15]. Like conventional RGD peptides, iRGD homes to tumors by initially binding to av integrins that are specifically expressed on the endothelium of tumor vessels. IRGD is then proteolytically cleaved in the tumor to

produce CRGDK/R. The truncated peptide loses much of its integrin-binding activity, but gains affinity for neuropilin-1 (NRP-1) because of the C-terminal exposure of a conditional C-end Rule (CendR) motif (R/KXXR/K). The NRP-1 binding triggers tissue penetration, which is tumor-specific because the cleavage requires earlier binding of the peptide to integrins. These features confer on iRGD a tumor-specific tissue penetration activity.

Strategies for Anticancer Drug Delivery using Peptide Drug Conjugates:

Non peptidic small molecules target the new G – protein coupled receptors which are small molecules for targeting peptides which binds receptors on cancer cells. The idea is to use antagonist that block the pro malignant affects of peptide receptors signaling pathway. This strategy can be used in the treatment of non tumor cell lung cancer. Epidermal Growth Factor Receptors (EGFR) is already approved for this treatment. Several small molecule drug conjugates for cancer therapy have been developed, where most of them address plasma membrane associated enzymes, transported proteins or cell surface receptors that are not peptide receptors. One of the best studied classes of Small Molecule Drug Conjugates (SMDCs) are compounds that target foliate receptor especially in the treatment of ovarian cancer. The non peptide ligands are also developed as tools for the imaging (diagnostic purpose) of over express peptide binding receptors on tumor cells [6].

Antibody-Drug Conjugates (ADCs) have emerged as a platform for targeted cancer therapy, reflecting their extended circulation in blood and skill to deliver highly cytotoxic cargo specifically to focus on cancer cells, resulting in potent therapeutic efficacy. Although a couple of ADCs have already been successfully utilized in the clinic, there are several drawbacks to using an antibody as an escort molecule for delivering drugs to tumors. These include limitations in production techniques, which generate a heterogeneous mixture of ADCs with variable numbers of medicine attached; the high cost of ADC manufacturing and quality control; and poor penetration of ADCs deep into tumor tissue, due to the massive size of the conjugated antibody, which limits their therapeutic efficacy, especially in solid tumors. As alternatives to ADCs, a number of cancer-targeting peptide drug conjugates using somatostatin, bombesin, CRGD, and aptides have been explored for targeted cancer therapy. Unlike ADCs, PDCs can be synthesized cost-effectively in large scale as a single chemical entity [16]. Additionally, the much smaller size of PDCs should allow them to penetrate deeper into the tumor than do ADCs. However, a critical drawback of PDCs is their far shorter circulation half-life compared with ADCs, due to rapid renal clearance, limiting therapeutic efficacy.

Advantages of Peptide Ligands as Cargos for Anti Cancer Drug Delivery

Peptide ligands are a highly suitable choice for the planning of drug conjugates that address peptide-binding receptors. They comprise several advantages as carrier molecules for delivery of the therapeutically active moieties to cancer cells. Peptide ligands usually bind with the high affinity to their target receptors, which allows the use of low dosages of the Peptide-Drug Conjugate (PDC) to obtain an efficient therapeutic effect. The peptides are considered as safe, and they have low immunogenicity and produce nontoxic metabolites. Peptides up to 50 amino acids are often readily synthesized by solid-phase peptide synthesis and selectively equipped with complex modifications to get PDCs with advanced features. A drawback of peptide ligands as drug delivery systems can be their poor in vivo stability and short half-life, owing to their fast degradation by the proteolytic enzymes in blood and rapid renal clearance. Hence, the natural peptide hormones of peptide receptors often need to be stabilized. This can be accomplished by backbone and sequence-modification, which is usually used for the planning of PDCs. Modifications include, for example, cyclization, N-methylation, and amino acid substitutions with unnatural or D-amino acids. Another important approach to increase the half-life of pep tides for therapy is lipidation. The attached carboxylic acid moiety is in a position to bind to human albumin within the blood stream, which features a protective effect and results in a extended circulation time of the peptide conjugate [6]. This concept is impressively demonstrated for the marketed, long-acting glucagon-like peptide-1 (GLP-1) receptor agonists, which are used for the treatment of type 2 diabetes. Lipidation are often therefore also useful for the generation of PDCs with enhanced half-life. A longer circulation of PDCs is usually required for the treatment of solid tumors to permit sufficient time for delivery and penetration of the PDC into the malignant tissue. In some cases, however, persistence of PDCs in circulation might cause stronger side effects thanks to extended exposure of tissues to the toxic agent. Overall, tailoring of the pharmacokinetics of PDCs remains one of the major challenges for clinical translation of these molecules.

Targeting Peptides

Modern molecular biology has dramatically facilitated the discovery of hundreds of cancer targets [9, 12]. Playing roles in the cellular functions and intercellular communications, the peptide ligands are composed of a rosary-like assembly of amino acids connected by amide bonds containing usually but 100 monomers. Their low relative molecular mass allows a rapid clearance from the blood and non-specific binding sites, and their high specificity leads to active concentration as low as nano-molar range. Interestingly, peptide ligands are often considered highly flexible regarding their chemical composition. Indeed, modifications like cyclization, unnatural amino acids or their combinations linked with chemical linkers are often easily achieved.

The targeting peptide sequence are often determined via different techniques. These include the event of derivatives inspired by the natural protein sequences e. g. vascular endothelial growth factor, VEGF and somatostatin (SST) or screening of peptide libraries composed of billions of short random amino acid sequences ultimately displayed on viral particles. This phage display technique was first reported in 1985 using genetically engineered filamentous DNA-containing bacterial viruses (phage) that were modified to precise foreign aminoalkanoic acid sequences as a part of their protein coat. A decade later the primary in vivo screening of peptides selectively homing to brain and lungs was performed. Since then the icosahedra T7 phage system

has been introduced to display peptides as a fusion of its capsid protein [10].

Targeting Peptides Derived from Natural Ligands:
The usage of a targeting ligand is usually motivated by the overexpression of tumor-specific receptors. The accumulation of targeting homing peptide within tumors correlates with the receptor expression allowing the discrimination of the abnormal from the traditional tissue. Therefore, the peptides conjugated to imaging moieties are diverse as fluorescent dyes, radionuclides or iron-oxide particles that is respectively used for the optical, Positron Emission Tomography or Single Photon Emission Computed Tomography (PET or SPECT) as well as Magnetic Resonance Imaging (MRI) [10]. The recent emergence of theragnostic tools suitable to be used both in imaging and therapy transcends the borders between the 2 disciplines.

Somatostatin (SST) Derivatives:
Many solid cancers are frequently related to aberrant overexpression of the G Protein-Coupled Receptors (GPCR) activated by peptide ligands, including the Somatostatin Receptor (SSTR) family [10]. The SSTR family comprises five receptors (SSTR1 to 5) cosmopolitan within the central systema nervosum, pituitary, and lots of peripheral organs. Binding of the natural ligand somatostatin peptide (SST) to the receptors leads to inhibition of proliferation and/or induction of apoptosis in cancer cells.

Peptides Targeting the Tumor PH and Temperature
Within the tumor tissue, the deregulated angiogenesis / lymphangiogenesis related to a high rate of the neo plastic cells results in insufficient clearance of metabolic acids and a gradual decrease in the pH in tumor microenvironment [17]. This has led to development of pH-sensitive drug-delivery systems, like the pHLIP (pH-Low Insertion Peptide). pHLIP is a 36 residues long peptide derived from the bacteriorhodopsin C helix and able to insert into cell membranes as an a-helix only under low pH conditions whereas a basic or neutral pH environment results in a loss of the helical structure and decreased affinity towards the membranes Fig.3

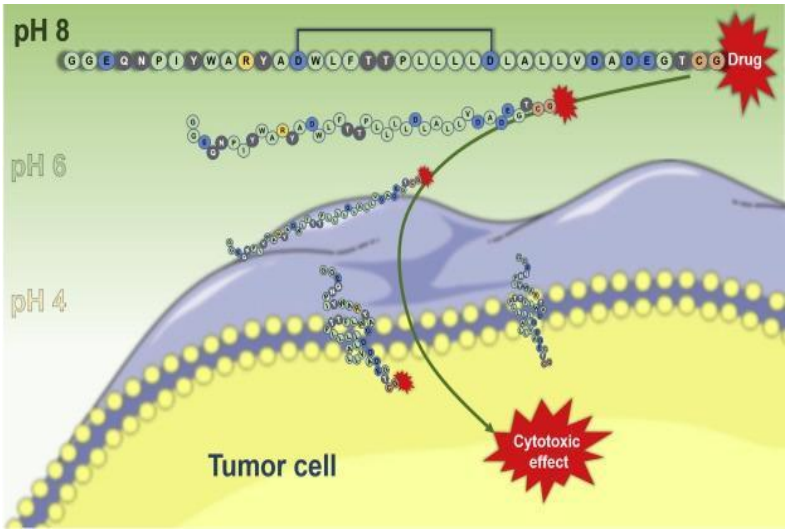

Figure 3: Modality of the pHLIP peptide binding to the tumor cell membranes with subsequent local drug delivery. At basic/neutral pH, the peptide is unstructured and can be partly found associated but not inserted into biological membranes. At low pH, PHLIP will become fully inserted into the lipid membranes and exhibit an a-helical structure. This change in conformation is due to the binding of acid protons on the two aspartic acids (D) highlighted by a bridge on the peptide sequence. Moreover, the C-terminal C residues can be used for drug conjugation.

The intra-tumoral mild hyperthermia is another targetable characteristic of the tumor microenvironment [9, 10]. The aberrant endothelial cell proliferation leads to malfunctional vessel network that limits the general heat exchange usually provided by a correct blood flow. Thus, this local characteristic of the tumor microenvironment compared to the encompassing tissues are often wont to trigger peptide formulations to reply accordingly.

Cationic Antimicrobial Peptides (CAPs)
Cationic antimicrobial peptides (CAPs) are agents that exhibit both antimicrobial and anti – cancer activities due to their cationic characteristics, which are cytotoxic to cancer cells [12]. The innate immune system includes small molecules called antimicrobial peptides (AMPs), which have 1–10 kDa of molecular mass. AMPs can be isolated from nature, and it is possible to modify their structure to increase their potency, efficiency, and selectivity [9]. Due to a high content of basic amino acids, AMPs have an overall positive net charge and typically have an amphipathic structure that permits them to interact with the bacterial membrane. AMPs used in cancer treatment should be able to affect cancer cells without affecting normal cells. The electrostatic interactions between AMPs with a positive charge and cancer-cell membranes with a negative charge lead to cytolysis and to the selective killing of the cancer cells.

Tumor Homing Peptide
Tumor homing peptides (THP) are produced using the method of in vivo phage display [12]. THP is peptides with specific affinity toward components of the tumor microenvironment, such as tumor endothelium, lymphatics or tumor cells. THPs are extensively utilized as targeting entities, to direct chemotherapeutics, diagnostic or imaging

compounds to tumor tissue. THPs, offer an advantage of smaller size and better tissue penetration. Tumor-homing peptides (THPs) selectively target cancer and cancer-associated microenvironments, thereby leading to a selective transfer of therapeutic drugs for cancer treatment. Cancer cells express specific markers on their surfaces, which distinguishes them from normal cells. Because of their binding to special receptors, THPs can be used for the targeted delivery of the drugs. However, problems related with the use of THPs include immunogenicity possibility as well as nonspecific cytotoxicity must be considered. In many recently reported studies about system and a consequent immunological reaction within the organism, no general immune reaction was reported.

Peptide Type	Target, Activity	Role	Additional Components Needed
ACP	Intracellular activity in cancer cells	Therapeutic	Intrinsic activity, needs to have CPP activity or needs addition of CPP
THP	Extracellular binding in tumor tissue	Diagnostic (therapeutic)	No intrinsic activity, can be used as a targeting entity or a therapeutic, if CPP and drug added
PPI mimicry	Intracellular activity in cancer cells, harmless in normal cells	Therapeutic	Needs addition of CPP
CPP	No activity in cells	Drug delivery	Needs additional targeting and drug component
Peptide hormone	Extracellular binding target	Therapeutic	No additional component needed, intrinsic activity

Chimeric Peptides

Anti-cancer drug can be produced by the fusion of two peptides with different modes of action. The combination of a homing peptide that induces a selective binding to cancer cells with a killer peptide that results in the destruction of cancer cells makes a chimeric peptide which will destroy cancer cells selectively and efficiently. A homing peptide which will selectively enter cancer cells, tumor blood vessels, and lymphatic vessels are often isolated employing a technique like a phage display. The homing peptide within the structure of a chimeric peptide results in its selective delivery to cancer cells; the utilization of a killer peptide is simpler in reducing potential side effects. CAPs are often used as killer peptides, which may disrupt the mitochondrial membrane and thus induce apoptosis in cancer cells by causing irreversible damage to the mitochondrial membrane. The activity of CAPs is not dependent on interaction with specific receptors; they do not have the resistance problems of traditional therapies [18, 9].

Targeting peptides identified by combinatorial screens:

Phage display may be a very powerful selection tool that has been widely wont to identify novel tumor homing peptides, most of which target the tumor-associated vasculature. One of the major advantage of phage display screens is that it does not require any knowledge about the tumor-specific differences and that selects peptides homing and bind to the receptors that are accessible for binding in an unbiased way. These homing peptides have then been wont to identify novel tumor-associated molecules and as results in develop novel targeting agents [9, 12].

Tissue-penetrating peptides:

Some of the tumor targeting peptides, just like the LyP1, exhibit cell penetrating properties and are ready to internalize cells during a cell type specific manner. It was reported that peptides sharing the (CendR) motif induce both cellular uptake and tissue penetration through interaction with neuropilin-1 (NRP-1). The prototypic tumor-penetrating, cyclic peptide iRGD binds both Oly integrins and NRP-1 and has been shown to significantly inhibit tumor metastasis in vitro by provoking the detachment and subsequent death of human prostate cancer cells anchored to fibronectin [19].

Peptides Targeting malignant brain tumors:

The central systema nervosum may be a closed territory, delimited by a physical border i. e. the skull bone and meninges tissue, and a cellular/molecular limitation personified by the BBB that rigorously selects the nutrients, macromolecules, and drugs able to diffuse into the brain parenchyma [9, 19]. Recently, novel targets are discovered for malignant brain tumour imaging and drug delivery. A novel 9 amino acid long, linear targeting peptide called COOP that binds the Mammary-Derived Growth Inhibitor (MDGI) highly expressed by various cancers including a subset of breast cancers and invasive brain tumors was identified by using the phage monitor.

Application of Peptides in Cancer Treatment

Peptide Hormones

Formulations of Luteinizing Hormone Releasing Hormone (LHRH) agonists like buserelin, leuprolide, goserelin, and triptorelin are developed for more efficacious and convenient treatment of patients with the prostate cancer. Administration of these peptides causes the down regulation of LHRH receptors within the pituitary, leading to an inhibition of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) release, and a concomitant decrease in testosterone production. Discovery of LHRH antagonists leads to therapeutic improvement over agonists as they cause dose-related inhibition of LH and FSH by competitive blockade of the LHRH receptors. Cetrorelix was the primary LHRH antagonist given marketing approval and, thus, became the primary LHRH antagonist available clinically [8]. Subsequently new generation LHRH antagonists like abarelix and degarelix are approved for human use.

Peptide as Radionuclide Carrier

Apart from the use of peptide-based LHRH hormones Somatostatin Analogues can be used in Cancer Therapy and Peptide Receptor Radionuclide Therapy (PRRT). Analogues of somatostatin (peptide hormone consisting of 14 amino acids, found in δ cells of the pancreas also as in hypothalamic and other gastrointestinal cells) such as octreotide (sandostatin), lanreotide (somatuline), is employed within the management of acromegaly and symptoms caused by neuroendocrine tumors, most notably carcinoid syndrome and VIPomas [8].

PRRT combines octreotide (or other somatostatin analogs) with a radionuclide which may be a radioactive substance and form highly specialized molecules called radiolabeled somatostatin analogues or radiopeptides [20]. Radiolabeled somatostatin analogs generally comprise three main parts: a cyclic octapeptide (e. g., octreotide), a chelator (e. g., DTPA or DOTA), and a radioactive element (111In, 90Y, or 177Lu). These radiopeptides are often injected into a patient and can travel throughout the body binding to carcinoid tumor cells that have receptors for them. Once bound, these radiopeptides emit radiation and kill the tumor cells they're sure to (Fig: 4)

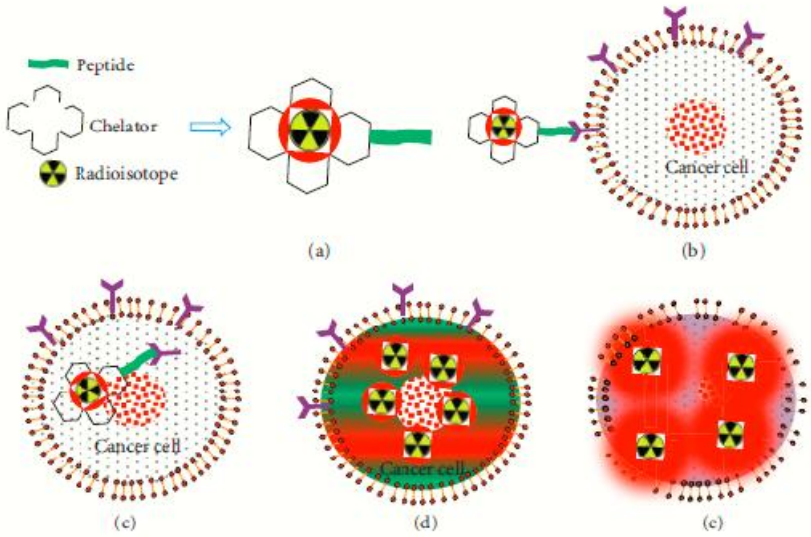

Figure 4: Peptide receptor radionuclide therapy (PRRT); radiolabeled somatostatin analogs generally comprise three main parts: a cyclic octapeptide (e. g., Tyr3-octreotide or Tyr3-octreotate), a chelator (e. g., DTPA or DOTA), and a radioactive element. Radioisotopes commonly used in PRRT are 111In, 90Y, and 177Lu

Peptide Vaccines: Active immunization is the promising strategies to treat cancer. The vaccination method for treating cancerous cells relies on the vaccines consisting of peptides that derived from the protein sequence of tumor-associated or specific antigens. Tumor cells express antigens known as Tumor-Associated Antigens (TAAs) that can be recognized by the host's immune system (T cells) [8]. These TAAs can be injected into cancer patients to induce a systemic immune response that may result in the destruction of the cancer cells growing in different body tissues. This procedure is defined as the active immunotherapy or vaccination because the host's system is either activated de novo or re stimulated to mount an efficient, tumor-specific immune response that may ultimately lead to tumor regression (Fig: 5). Any protein/peptide produced in a tumor having an abnormal structure due to mutation can act as a tumor antigen. Such abnormal proteins are produced due to mutation of the gene [21].

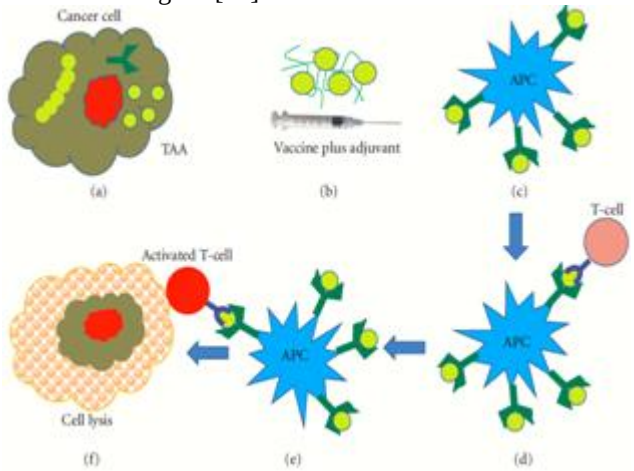

Figure 5: Peptide-based cancer vaccines: tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the host's immune system (a). These TAAs mixed with an adjuvant can be injected into cancer patients in an attempt to induce a systemic immune response (b). The antigen presenting cell (APC) presents the antigen to T cell ((c) and (d)), thereby the T cell is activated (e) which results in the destruction of the cancer cell (f).

The T-cell antigen receptor (TCR) on T cells recognizes the complex of a touch peptide located within the antigen-binding groove of an MHC molecule [21]. MHC molecules are subdivided into class I molecules, which are found on all nucleated cells and sophistication II molecules, which are found on specialized Antigen Presenting Cells (APCs) like dendritic cells, macrophages, B cells, and selected activated endothelial or epithelial cells. CD4+ T cells recognize antigens bound to MHC class II molecules and these class II molecules are expressed on APCs that possess the potential of antigen capture through phagocytosis or binding to surface antibody. The peptide vaccines are relatively less expensive, easy to manufacture and manipulate, are of defined structure, and being synthetic in nature do not have a haul of batch to batch variation. the most disadvantage of the peptide vaccines is their weak immunogenicity. Several strategies like epitope enhancement, use of various T-cell epitopes, adjuvants, incorporation of co stimulatory molecules, ex vivo loading into antigen presenting cells are being explored to strengthen the immunogenicity and efficacy of the peptide vaccines.

Peptide as Nanomaterial

Nanomaterial-based drug delivery systems have long been seen as particularly promising for cancer therapy thanks to

their great potential for improving drug specificity, biocompatibility, pharmacokinetic features, and antitumor efficacy. for several particulate-based drug carriers, the heterogeneity among tumor cells and thus the presence of complex stromal cell barriers are still great challenges limiting their tumor-targeting and penetrating performances, and strat egies to beat tumor heterogeneity and to interrupt stromal barriers are urgently needed [22]. Cancer-Associated Fibroblasts (CAFs), the predominant cell type within the tumor stroma, form a significant barrier that impedes penetration of nano particulate therapeutics and even molecular drugs into solid tumors. Compared to tumor cells that show diverse marker proteins among different tumor types, CAFs selectively overexpressed certain proteins, like Q-Smooth Muscle Actin (a-SMA) and Fibroblast-Activated Protein-a (FAP-a), in most solid tumors but not normal tissues. Consequently, development of smart nanomaterials responding to CAFs could even be a specific and efficient strategy to beat the aforementioned obstacles, leading to increased drug perfusion and improved antitumor efficacy.

Peptides and peptide derivatives, thanks to their biocompatibility, chemical versatility, and biological recognition abilities, are widely utilized as building blocks to construct soft functional biomaterials for specific applications, like tissue engineering and drug delivery. Extensive studies have signified that tailor-made peptides can self-assemble into unique secondary structures or nanostructures. Certain peptides derived from the degradation or cleavage of antibodies or collagens exhibit specific targeting capacity and therefore the enzymatic activity. These features render peptides extremely useful within the development of versatile, multi-functional, and stimuli-responsive nanostructures for drug delivery and release, especially in tumor tissues over expressing proteases.

Limitations of Peptides in Targeted Cancer Therapy

Even though the peptides have great potential in targeted cancer therapy, they have limitations like low stability in plasma, sensitivity to proteases, and conformational flexibility. In protein structures, the adjacent parts of peptide sequences are involved within the formation and stabilization of peptides. However, peptides do not have 3d structure and show randomness during which conformational isoforms interconvert to each other in nanosecond-time scales [23]. This conformational flexibility leads to non-specific interactions with different receptors. These non-specific interactions could even be viewed as side effects; therefore, a special approach to stabilizing peptide structures must be investigated [24]. The strategy for enhancing the conformational stability of peptides is peptide stapling which constrains a quick peptide sequence by using covalently linked side chains of two amino acids. Another strategy is peptide cyclization. This approach is additionally effective for decreasing sensitivity toward proteases and for increasing peptide's binding selectivity. Modification of N- and C-terminus leads to inhibitors of exopeptidases, amino peptidases, and carboxypeptidases, and should improve peptide stability.

2. Conclusion

The limitations of current cancer treatments that use small-molecule chemotherapeutic drugs necessitate the development of novel therapeutic options. Peptides display selectivity toward malignant cells, minimal immunogenicity, excellent tissue penetrability, low cost manufacturability and straightforward modification for enhancing in vivo stability and biological activity against cancer cells. The advancements within the rational design of peptide-based drugs using computational molecular modeling and combinatorial chemistry techniques, like phage displays and peptide microarrays, significantly increased the availability of libraries of targeted peptides with high affinity and specificity for somatic cell targets [25]. These characteristics make them ideal candidate for targeted antineoplastic drug discovery and development. The peptides appear to possess an honest capacity to be used directly or alongside other peptides and tiny molecule drugs for targeted cancer therapy [26]. Therapeutic peptides are often developed for inhibition or reactivation of a huge kind of important signaling molecules. These peptides are often specific for individual target proteins and in some cases, can also be specific for cancerous cell types.

Identification of targeting peptides has not only been inspired by the natural ligands, but also by using combinatorial screening of various libraries. Specific homing to any cancer marker is hypothetically possible using synthetic moieties, modified agonists/ antagonists additionally to the new peptides that are discovered using as an example the phage display technology. The phage display screening technique has provided many excellent peptides targeting different tumor-specific markers in an unbiased manner [10]. These therapeutic peptides exhibit high specificity, low antigenicity, flexibility, and rather simple production. Peptides represent possibilities for the development of better targeted imaging and therapeutic options for various solid tumors within the field of personalized medicine in cancer. In today's developing era of precision / personalized medicine the therapeutic peptides represent an exciting field of drug discovery and research. Modern molecular biology has enabled the discovery of hundreds of cancer targets and along with therapeutic peptides has revolutionized man's sustained fight to overcome cancer that till today represents the ultimate challenge of modern medicine.

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