

Anticancer peptide: Physicochemical property, functional aspect and trend in clinical application (Review)

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Abstract. Cancer is currently ineffectively treated using therapeutic drugs, and is also able to resist drug action, resulting in increased side effects following drug treatment. A novel therapeutic strategy against cancer cells is the use of anticancer peptides (ACPs). The physicochemical properties, amino acid composition and the addition of chemical groups on the ACP sequence influences their conformation, net charge and orientation of the secondary structure, leading to an effect on targeting specificity and ACP-cell interaction, as well as peptide penetrating capability, stability and efficacy. ACPs have been developed from both naturally occurring and modified peptides by substituting neutral or anionic amino acid residues with cationic amino acid residues, or by adding a chemical group. The modified peptides lead to an increase in the effectiveness of cancer therapy. Due to this effectiveness, ACPs have recently been improved to form drugs and vaccines, which have sequentially been evaluated in various phases of clinical trials. The development of the ACPs remains focused on generating newly modified ACPs for clinical application in order to decrease the incidence of new cancer cases and decrease the mortality rate. The present review could

further facilitate the design of ACPs and increase efficacious ACP therapy in the near future.

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1. Introduction

Cancer drug therapy was developed from chemotherapy and radiotherapy to molecular targeting therapy combined with a 'guiding missile', for cancer-targeted delivery to avoid healthy tissue damage (1). For example, in genome targeted therapy, DNAs and RNAs can interfere with the normal host genome, and genetic modification is difficult as the modified genes may mutate the original genome or the off-target (2). Furthermore, immunotherapy with antibodies against cancer cell surface antigens can provide specific delivery, but some healthy cells can express the same targeted antigens, resulting in limited effectiveness (3). Small molecules can also exert antitumor effects on cancer cells, such as C188-9, a STAT3 inhibitor, in head and neck squamous cell carcinoma, and GNS561, a lysosomotropic molecule, in intrahepatic cholangiocarcinoma (4,5). Moreover, these small molecules can be used in drug delivery systems (6); however, they are difficult to synthesize. Therefore, peptides against cancer cells are an alternative therapeutic method in anticancer drug development.

Anticancer peptides (ACPs): What and why? ACPs, as small peptides containing amino acid sequences, are selective and toxic to cancer cells (7). ACPs are a superior choice of therapeutics compared with antibodies and small molecules due to their high selectivity, high penetration and easy modifications (8-10). Ideally, anticancer therapy should destroy a range of cancer types, but not all healthy cells.

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Abbreviations: ACPs, anticancer peptides; AML, acute amyloid leukemia; FSH, follicle stimulating hormone; GHRH, growth hormone-releasing hormone; LHRH, luteinizing hormone-releasing hormone; LONp, lanthanide oxyfluoride nanoparticle; LY6K, lymphocyte antigen 6 complex locus K; PCNA, proliferating cell nuclear antigen; PPV, personalized peptide vaccination; ROS, reactive oxygen species; uPAR, urokinase plasminogen activator receptors; WT1, Wilms' tumor 1

Key words: therapeutic peptide, anticancer peptide, modified peptide, targeting peptide, cancer, clinical application, clinical trial

A different property between cancerous and healthy cells is the cell membrane. Numerous anticancer peptides destroy cancer cells via apoptosis and necrosis by membrane lysis or pore formation (11-13). The eukaryotic cell membrane contains cholesterol to protect lytic action by modifying membrane fluidity (14). Moreover, a high level of membrane cholesterol can inhibit lytic activity. It has been shown that membrane fluidity of cancer cells is higher compared with healthy cells (15). Cancer cells also contain more abundant microvilli compared with healthy cells, which increases the cell surface area (16). Furthermore, healthy cells have electrical neutrality, whereas cancer cells contain a negatively charge component on their surface (17), leading to membrane destabilization, cytotoxicity and cancer cell lysis when interacting with small molecules, such as ACPs (18,19). In addition, the primary driving force for the interactions between peptides and the healthy cell membrane is the hydrophobic interactions, while that between peptides and the cancer cell membrane is the electrostatic interactions (20).

Anticancer medicines contain molecularly targeted drugs with or without 'guiding missiles' to interact with specific molecular targets on cancer cells (21). Besides molecularly targeted drugs, drug-delivery to the cancer cell surface was developed using the most important properties, including high specificity, high selectivity and the binding capability to various targeted drugs, as well as being easy to synthesize and produce (21). Peptide properties can be used both in molecularly targeted drugs and 'guiding missiles' to inhibit cell proliferation or eradicate cancer cells completely, depending on the amino acid residue composition, sequence length, isoelectric point, molecular weight, net charge, hydrophobicity, amphiphilicity, secondary structure and structural orientation (22). These ideal anticancer peptide characteristics are summarized in Fig. 1. Membrane characteristics promote or inhibit drug penetration, drug conformation and/or location within the membrane and sequentially affect therapeutic targets (23). Healthy cell membranes have zwitterion phosphatidylcholine and sphingomyelin in an outer leaflet and anionic phosphatidylserine and the phosphatidylethanolamine in the inner leaflet with the asymmetric distribution (24). The inner leaflet with the asymmetric distribution is primarily maintained by flippases (phosphatidylserine and phosphatidylethanolamine from outer to inner membrane), floppases (phosphatidylcholine and cholesterol from inner to outer membrane) and scramblases (facilitated the flip-flop of lipids) (24,25). In contrast, the cancer cell membrane loses this asymmetric distribution and alterations in membrane fluidity, resulting in exposure of negative charge of phosphatidylserine on the surface of the membrane, as well as the locating of phosphatidylethanolamine on the outer leaflet (26-28). Furthermore, sphingomyelin is decreased in the cancer cell membrane and is associated with tumorigenesis (29). Different lipid composition affects membrane fluidity, influencing drug penetration and biological action (30,31). Extracellular acidity with or without exosome release affects the pH, changing from 7.4 to 6.5 (typical pH of cancer), forming the malignant tumor phenotype (32). The surrounding environment in the acidic extracellular pH (pHe) can promote cancer invasiveness (33). Specific interaction between anticancer peptides and cell membrane components are mostly bound by electrostatic interactions (34).

Anticancer peptides act as either molecularly targeted peptides, which can penetrate and directly bind to the specific cancer cell or organelle membranes, or binding peptides linking to the anticancer drugs (35-37). In cancer cells, anticancer peptides, as molecular targeting peptides, particularly in the α -helical form, penetrate the plasma membrane, the nuclear membrane and/or the mitochondrial membrane exerting pharmacological activity via different mechanisms (such as the inhibition of DNA synthesis or cell division), thus promoting cancer cell apoptosis (38-41). However, binding peptides, also referred to as cancer-targeting peptides or cell-penetrating peptides, that have no anticancer property, can recognize and penetrate the cancer cell membrane (42). Binding peptides can also be used for drug delivery by binding to the anticancer drugs, such as those that are non-penetrable (43).

Amino acid composition and derivatives in peptides also convey anticancer properties. Amino acid residues containing peptides can drive cell permeability (44-46). The amino acid residues that are predominant in peptides with anticancer abilities include glycine, lysine and leucine (47). For example, hydrophobic positively charged lysine- and arginine-rich peptides act as cationic peptides that can interact with membranes via a snorkeling mechanism, including selecting anionic membranes on cancer cells, disrupting cell membrane integrity, penetrating into the membrane and potentially serving a role in cancer cell toxicity (48). Moreover, protonation of histidine under acidic pH conditions means that histidine-containing peptides can induce cancer cytotoxicity via membrane permeability under acidic conditions (49,50). Glutamic and aspartic acid residues present potential anti-proliferative activity on the tumor cells (51). Cysteine residues in ACPs do not serve a role in the selectivity and toxicity for cancer cells, but cysteine-rich domains on a number of cell surface receptors can stabilize and maintain extracellular motif or domain structures (52).

Internal prolines in peptides are crucial for membrane interaction and conformational flexibility, which is the same as glycine residues (53). It has been reported that serine and glycine-free diets can slow tumor growth and enhance antiproliferative effects (54). Methionine, a moderately hydrophobic amino acid, does not serve a major role in ACPs, but its elevated levels can be consumed by cancer cells. Furthermore, a methionine-deficient diet causes a metabolic defect in cancer cells by arresting cancer cell proliferation (55). Phenylalanine, a strongly hydrophobic residue, is highly present in primary tumors and acts as a protective amino acid (56). Phenylalanine-containing peptides can also enhance the affinity for targeting the cancer cell membrane (57). Tyrosine and tryptophan are weakly hydrophobic amino acids; tyrosine does not serve a role in toxicity of ACPs, whereas tryptophan may exert a role in the toxicity of some ACPs against cancer cells such as indolicidin and trans-activator of transportation (TAT)-Ras GTPase-activating protein-326 peptides (19,58,59). However, synthesized peptides containing tryptophan and histidine may decrease cytotoxicity, while those containing tyrosine, phenylalanine or proline may be able to increase cytotoxic activity (60). The tryptophan position on the cell-penetrating peptides serves an important role in entering cancer cells, which subsequently involves an

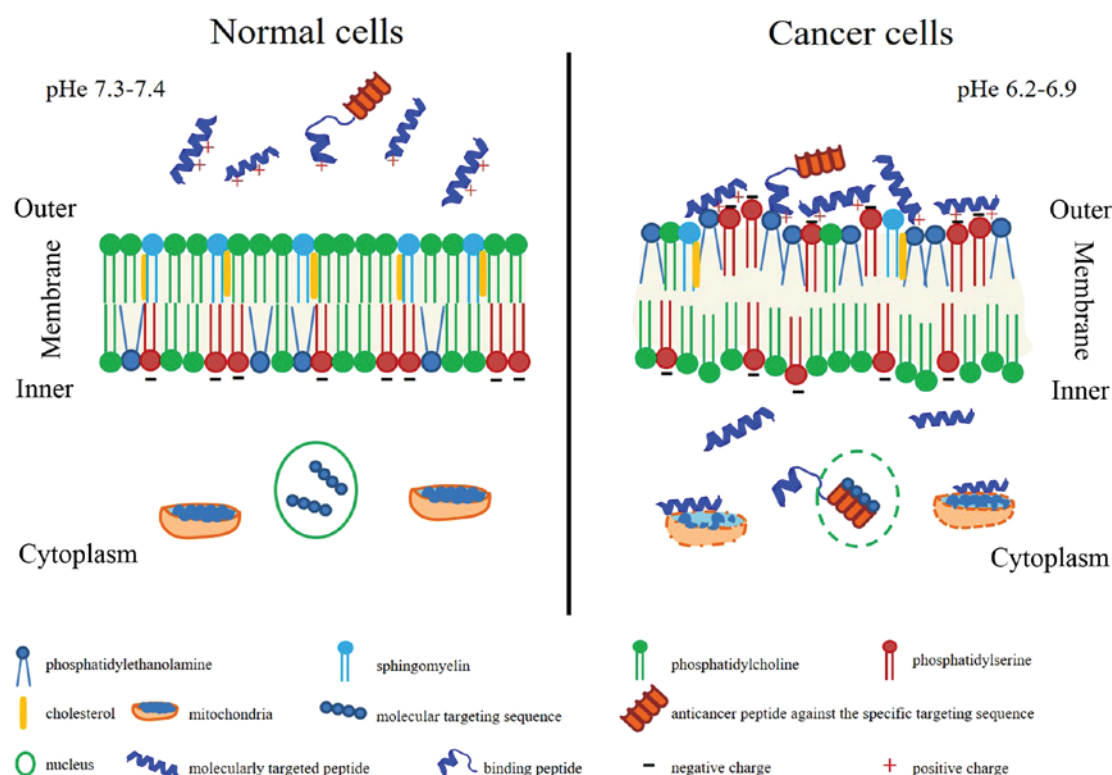


Figure 1. Comparisons of membrane characteristics and anticancer peptides action on healthy cells (left) and cancer cells (right). The outer leaflet of the healthy cell membrane presents a neutral net charge leading to non-interaction of anticancer peptides on the healthy cell surface (left), whereas negative net charge on the outer leaflet of the cancer cell membrane could interact with the cationic anticancer peptides (right). In cancer cells, anticancer peptides, particularly in the α -helical form, act as molecularly targeted peptides that can penetrate and directly bind to the specific cancer cell or organelle membranes promoting cancer cell apoptosis. While, binding peptides linking to the anticancer drugs that have no anticancer property, can recognize and penetrate the cancer cell membrane. pH, extracellular pH.

endocytic pathway and binding at the major groove of nuclear DNA (61). The role of amino acid residues on ACPs and on cancer cells is summarized in Table I. Collectively, these findings suggested ACPs should contain cationic and hydrophobic amino acid residues to further form secondary structures that affect cancer cells.

ACPs and the structure-activity relationship (SAR). The association between ACPs and SAR has been investigated and analyzed using machine learning, and it has been demonstrated that the majority of ACPs contained 21-30 amino acids and were predominately composed of glycine, lysine and leucine (47). In addition, amino acid residues on a peptide influences its anticancer activity depending on the cationic, hydrophobic and amphiphilic properties associated with forming helical structure (62-64). Anticancer activity is primarily determined by the IC_{50} value associated with cancer cell membrane disruption (62). It has been reported that peptides with a higher hydrophobicity can penetrate into the hydrophobic core of the cancer cell membrane, resulting in cancer cell disruption via necrosis (62). Several studies have aimed to substitute low hydrophobic and neutral or acidic amino acid residues with positively charged amino acid residues, such as lysine and leucine, on the polar and non-polar faces of α -helical peptides (63,65). As a result, high cationic peptides with moderate hydrophobicity can enhance the cytotoxicity of cancer cells (63). Peptides in free-form do not fold in solution, but arrange in an α -helix or β -sheet

via electrostatic interaction on the membrane surface of the cells (11).

As well as the physicochemical properties, the secondary structure of the peptides is important in cell surface interaction, such as peptide structural orientation (57). The orientation of peptides can enhance the surface-activity for targeted interaction with the cancer cell membrane (66). The angle of the interaction leads to destabilized lipid packing on the cancer cell membrane, thus resulting in membrane penetration (67). Furthermore, modifying peptides by adding chemical groups, including methylation, acetylation or phosphorylation (particularly phosphorylation at tyrosine), can inhibit STAT3 phosphorylation, leading to cancer cell death (68). The potential modification of natural peptides is presented in Fig. 2. Therefore, the results indicated that the secondary structure of ACPs serves a crucial role in peptide-cancer cell membrane interaction, leading to cancer cell disruption and cell death.

2. Classification of ACPs

Anticancer peptide creation should consider the peptide structure, mode of action, selectivity and efficacy to specific cancer cells (69,70). In the present review, active peptides were classified into three types depending on their actions, including: i) Molecularly targeted peptides, which directly act on cancer cells via cytotoxic, anti-proliferative and apoptotic activities; ii) 'guiding missile' peptides or binding peptides, which are drug binding peptides used for transporting drugs

Table I. Role of amino acid residues on ACP effects in cancer cells, based on previous reports.

Amino acid residue	Amino acid properties	Action on cancer cells	(Refs.)
Charged residues on ACPs			
Lysine	Positively charged	Disrupt cell membrane integrity and penetrate cell	(48)
Arginine	(basic amino acids),	membrane, leading to cancer cell cytotoxicity	
Histidine	polar, hydrophilic	Induce cancer cytotoxicity via membrane permeability under acidic condition	(49,50)
Glutamic acid	Negatively charged	Antiproliferative activity on tumor cells	(51)
Aspartic acid	(acidic amino acids), polar, hydrophilic		
Effect on cancer cell structure			
Cysteine	Polar, non-charged	On numerous cell surface receptors for stabilizing and maintaining extracellular motif/domain structure	(52)
Proline	Non-polar, aliphatic residues	Membrane interaction and conformational flexibility, may be able to increase cytotoxic activity	(53,60)
Glycine		Membrane interaction and conformational flexibility	(53)
Phenylalanine	Aromatic	Enhance the affinity for target cancer cell membrane, act as protective amino acids of primary tumors and may be able to increase cytotoxic activity	(57,60)
Effect on cancer cell metabolism			
Methionine	Polar, non-charged	Reduced methionine will arrest cancer cell proliferation	(55)
Tyrosine	Aromatic	May be able to increase cytotoxic activity	(60)
Tryptophan		Serve a role in the toxicity of some ACPs to cancer cells, entering cancer cells following an endocytic pathway and then binding at the major groove of nuclear DNA	(19,61)

ACP, anticancer peptides.

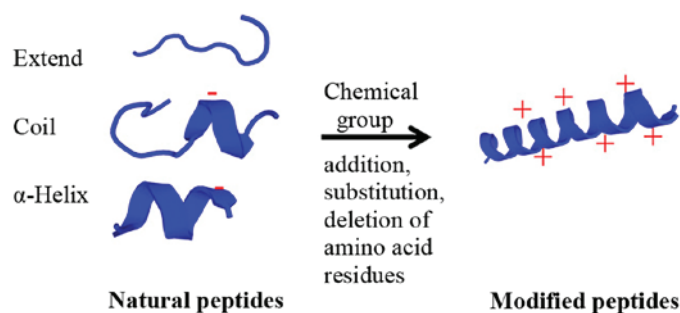


Figure 2. Modification of natural peptides. The natural peptide conformations included the extended, the coiled and/or the α -helical forms with neutral, anionic or cationic properties. These natural peptides are modified by adding the chemical groups (such as acyl and methyl groups) or the positive amino acid residues (such as lysine and arginine) to increase positive net charge and specificity for cancer cell targets. Moreover, the addition, deletion or substitution of the amino acid residues changes the conformation from the extended or coiled peptides to the α -helix form for higher cancer cell penetration. After modification, the cationic α -helix modified peptide exhibits higher efficacy and specificity to the cancer cells.

into the cancer cell targets; and iii) cell-stimulating peptides that indirectly effect other stimulating cells to kill cancer cells, such as via immunomodulatory activities and hormone receptors (71-73).

Molecularly targeted peptides. Molecularly targeted peptides, which are specific to the cancer cell targets, can penetrate, bind and then inhibit or kill cancer cells that are in an important stage of carcinogenesis or proliferation (74). The peptides concerning target cells can be classified into two major groups, including:

i) Peptides against only cancer cells, and not against healthy cells (75,76) and, ii) peptides against both cancerous and healthy cells (77). Numerous peptides have selectivity for cancer cells but not healthy cells, such as peptides derived from defensins, lactoferricin B, cecropins, magainin-2 and chrysopsin-1 (22).

The majority of ACPs are collected using the CancerPPD resource for predicting peptide structure and identifying the best ACP for further study (7). In addition, ACPs are identified via computational methods that consider amino acid composition, binary profiles and sequence-based methods (78-80).

Membranolytic ACPs are generated *de novo* using automated designs based on α -helical cationic amphipathic peptide sequences against the cancer cells (81). Anionic molecules in the malignant cells conferring a net negative charge are different from the normal mammalian cell membrane, which have a neutral net charge (17). High cholesterol contents in healthy cells can obstruct the cationic peptide entry via cell fluidity; healthy cells are less fluid compared with cancer cells (15,82). Furthermore, peptides can permeate into the cells, causing mitochondrial swelling with cytochrome c release, followed by apoptosis (83). For example, Mastoparan I, a peptide with a α -helical structure, can act on the negative charge of prostate and liver cancer cell surfaces causing cell injury, cell swelling, cell bursting and then necrosis (84). Moreover, SVS-1 (KVKVKVKV^DP-PTKVKVKVK-NH₂), as a β -sheet structure, disrupts cell membranes via pore formation in lung-, epidermal- and breast-cancer cells (85,86). Peptides extracted from marine organisms, such as sponges, mollusks, tunicates, bryozoans, algae, fish, soft corals and sea slugs, can act against human cancer cells via, for example, anti-proliferative, cytotoxicity and anti-tubulin activities, as well as suppressing microtubule depolymerization (87).

Amino acid composition of the peptides can act directly against various cancer cell types. For example, highly cationic peptides can enhance cancer cell specificity, while an increase in hydrophobic peptides can decrease the degree of specificity (63). Moreover, polycationic peptides have selectivity against human acute T-cell leukemia via a higher membrane potential compared with healthy cells (88). Lysine and arginine-rich peptides with an intact amphipathic helical interface can also enhance cell lysis via membrane lysis mechanisms by penetrating and inducing caspase-3-dependent apoptotic cell death (89). The methods of peptide designing, such as cyclization, hybridization, fragmentation and modification, have potential advantages in increasing drug half-life time in plasma, enhancing stability and activity and decreasing toxicity of ACPs, for improving their therapeutic efficacy (90).

Therapeutic peptides are classified into three classes based on the mechanism of peptide entry into cancer cells, including: i) Pore-forming peptides, which bind to negatively charged molecules on the cancer cell membrane for inducing apoptosis or necrosis; ii) cell-penetrating peptides, which translocate across the plasma membrane and transporting small molecules to oligonucleotides or proteins, known as internalization; and iii) tumor-targeting peptides, which bind to receptors on the cancer cell surface for cell internalization (91). Based on the mechanism of entry, therapeutic peptides are also classified into three groups based on their biological targets, including: i) Signal transduction pathways; ii) cell cycle regulation; and iii) cell death pathways (92,93). For instance, a tumor-penetrating peptide, KLA, exerts pro-apoptotic activity, which disrupts the mitochondrial membrane, leading to programmed cell death in tumors (40). In a tumor suppressor mechanism, kisspeptin-1 metastasis suppressor, a precursor for several shorter peptides, which regularly exhibits decreased expression in metastatic tumors, can suppress colonization of disseminated cancer cells in distant organs and is involved in mechanisms of tumor angiogenesis, autophagy and apoptosis regulation in breast cancer (94). Furthermore, the tubulysin analogue KEMTUB10 can inhibit tubulin polymerization during mammalian cancer

cell proliferation, block the G₂/M phase of the cell cycle and stimulate apoptosis or cell death via p53, Bcl-2-interacting mediator of cell death and Bcl-2 (95). Although ACPs can induce cancer cell death and specify an expressed molecule to cellular targets, such as a cationic anticancer peptide, temporin-ICEa and melanoma cell surface-expressed phosphatidylserine (96), ACPs have limitations, including drug binding peptide delivery to cancer cell targets (97). Thus, ACPs could be developed for their high penetration into the tumor tissue and tumor cells, as well as high antitumor activity (40). While ACPs can progress from binding to killing cancer cells, in terms of molecular targeting peptides, ACPs cannot be specific or penetrated all cancer cell types, leading to the need for an addition of a binding cancer cell target, such as 'guiding missile' peptides or binding peptides.

'Guiding missile' peptides or binding peptides. Optimizing anticancer drug delivery requires the safety of healthy cells, as well as cancer cell elimination (98). 'Guiding missile' peptides or binding peptides, used as delivery carriers, should hold the poorly stable, non-soluble drugs and control drug-release inside the tumor environments (99). Furthermore, these peptides require specificity, affinity and dose effectiveness (98). Anticancer drug concentration is continually diluted during transport until reaching the target areas. However, drug binding adjuvant and nanoparticles can retain drug concentration during transport to target areas and induce the slow-release of the drug at these target areas (100,101).

Drug concentration and cell and tissue barriers are an obstacle for therapeutic efficacy. Medical application for drug delivery requires biologically active conjugates (cargoes) and/or binding peptides ('guiding missile') to reach specific intracellular targets (102-104). Minimal amino acid sequences of various cell-penetrating peptides, typically comprising 5-30 amino acid residues, especially cationic residues, can pass through tissue and cell membranes using energy-dependent or -independent mechanisms without the interaction of specific receptors (36). Binding peptides can bind to the cargoes with either covalent (mainly disulfide and thioester bonds) or non-covalent bonds (electrostatic and/or hydrophobic interactions between negatively charged cargoes and positively charged peptides) to protect the cargoes from enzymatic degradation (105).

The physical and chemical properties of binding peptides can be categorized into three main classes: Cationic, amphipathic and hydrophobic peptides (42). Firstly, cationic peptides contain highly positive net charges comprising lysines and arginines. Arginine contains a guanidine head group, which is used to form bidentate hydrogen bonds with the negatively charged carboxylic, sulfate and phosphate groups on the cell membrane, resulting in binding peptide internalization into the cells; however, lysine does not contain the guanidine head group, leading to lower penetration into the cell membrane (106). Secondly, amphipathic peptides, which contain both hydrophilic and hydrophobic amino acids, are classified into primary (covalent binding hydrophobic domain targeting to cell membrane and nuclear localization signal), secondary (α -helical structure with hydrophilic and hydrophobic residues on different sides of the helix or β -sheet for cellular internalization) and proline-rich (pyrrolidine ring without hydrogen bonds on α -amino group able to allow

cell permeability) peptides (107,108). Hydrophobic peptides contain non-polar amino acids with a low net charge and have a high affinity for the hydrophobic domain of the cell membrane, leading to cellular internalization and translocation across the membrane via energy-independent mechanisms (107,109).

Binding peptides enter target cells via cell penetration (pore formation and membrane destabilization) and endocytosis (macropinocytosis, clathrin or caveolin-mediated endocytosis, and clathrin/caveolin-independent endocytosis with enhanced endosomal escape from a lysosome) depending on physico-chemical properties, size and concentration of the peptides (110). There are various mechanistic studies examining binding peptides depending on their targets. For example, D-form octa-arginines stimulates the intestinal epithelial transport of drugs, such as insulin, via energy-independent unsaturable internalization (111). Furthermore, a specific peptide derived from nuclear localization signal (NLS) and epidermal growth factor receptor pathway substrate 8 (EPS8), called CP-EPS8-NLS, can cross the cellular membrane and interfere with the nuclear translocation of EPS8, leading to inhibited cell viability and proliferation in acute myeloid leukemia (AML) (112). It has also been revealed that cell-penetrating peptide TAT-conjugated gambogic acid promotes tumor apoptosis via reactive oxygen species (ROS)-mediated apoptosis by increasing the ROS level in bladder cancer cells (113).

Development of cell-permeable therapeutic peptides with polar side chains has used advantage of adding methyl groups, asparagine residues and D-amino acids (45). Similarly, another drug delivery system, known as nanoparticles, can carry ACPs to tumor sites without enzymatic degradation and can then enter inaccessible tumor sites (114). However, anticancer drug-carrying nanoparticles should be optimized for synergistic effect, drug release control, circulating stability and drug combination (115). Moreover, binding peptides could be modified to protect enzymatic digestion, penetrate cancer cell or organelle membranes, specifically bind to cancer targets and stimulate biological cells around tumor environments (116).

Cell stimulating peptides

Immune system stimulating peptides. Host defense mechanisms against pathogens or transformed cells, such as the cancer cells, is a novel therapeutic approach that involves recruiting the immune cells into the tumors (117). Antigenic peptide-human leukocyte antigen class I complex respond to cytotoxic CD8⁺ T-cells against malignant diseases and brain tumors (118). However, ACP-produced vaccines exhibit poor immunogenicity, and thus require adjuvants to increase specific immune responses (119). For example, E75 peptide breast cancer vaccine (Her2 p369-p377) containing polyactin A can increase CD4⁺ and CD8⁺ T lymphocytes, enhance proliferation of splenocytes and increase levels of interferon- γ in splenocytes (120). Furthermore, a melittin-RADA₃₂ hybrid peptide hydrogel-linked doxorubicin can recruit activated natural killer cells in the primary melanoma tumor, resulting in growth retardation, as well as activation of dendritic cells of draining lymph nodes and production of cytotoxic T-cells against the remaining tumors (121). Tyrosinase-related protein 2 melanoma antigen peptide nanovaccine combined with CpG adjuvant could slowly result in growth of the melanoma tumor (122). Moreover, the 5-mer peptide, A-P-D-T-R, is a potential target

for immunotherapy against breast cancer due to its highly immunogenic property that exists within the variable number of tandem repeats found in all mucins, particularly mucin1, which is increased by 10-fold in adenocarcinomas (123). Some peptide vaccines have been studied in phase I/II clinical trials (124-126). For instance, an adjuvant multi-peptide vaccine (UroRCC) was administered in patients with metastatic renal cell carcinoma following metastasectomy (127). Furthermore, a multi-peptide vaccine (IMA950) containing 11 tumor-associated peptides, which targets IMA950 antigens, has been used as a tumor-targeting vaccine involving the T-cell response in grade II and III glioma (128). In metastatic hormone-naïve prostate cancer, the novel human telomerase reverse transcriptase (hTERT) peptide vaccine UV1 can induce an immune response, affecting the prostate-specific antigen level (129). A vaccine containing peptides can also be an adjuvant for activating the immune system. For instance, Hp91 peptide has formed the adjuvant for a protein vaccine against human papillomavirus to control cervical cancer (130). Therefore, immune system stimulating peptides are an alternative cancer therapy to control metastasis and eradicate cancer cells by activating host immunity with the specific tumor antigens.

Hormone stimulating peptides. The therapeutic peptides can inhibit cancer cell proliferation by controlling hormone release via their receptors (131). Cancer cells can produce hormones, such as growth hormone-releasing hormone (GHRH), to stimulate the pituitary gland and then the release of growth hormone (132,133). In a previous study, a GHRH antagonist was synthesized to inhibit proliferation in AML cell lines, including K562, THP-1 and KG-1a cells (134). Follicle stimulating hormone (FSH), for which the circulating level is increased by leptin, serves an important role in the initiation and the proliferation of the ovarian cancer cells (135). Moreover, the obese OB3 peptide, a derivative of leptin, may prevent leptin-induced ovarian cancer cells by disrupting leptin-induced ovarian cancer cell proliferation signal via stimulation of STAT3 phosphorylation and estrogen receptor α -activation (135). Furthermore, nanoparticle drug vehicles containing 21-amino acid peptides [YTRDLVYGDPAAPGIQGTGTF (D-FP21)] conjugated to polyethylenimine and methoxy polyethylene glycol target the FSH receptor, leading to anti-proliferative effects on ovarian cancer (136). For chemotherapeutic improvement of metastatic hormone-refractory prostate cancer, it was found that the AlkB homolog 2 proliferating cell nuclear antigen (PCNA) interacting motif peptide targeting PCNA, an essential scaffold protein, in combination with docetaxel could decrease prostate volume and inhibit cancer cell regrowth *in vivo* (137).

3. Development of therapeutic ACPs

The issues with conventional therapeutic agents associated with the majority of cancer drugs, include poor water solubility, lack of target specificity and capability, non-specific distribution, system cytotoxicity and low therapeutic index, can be solved by creating a water-soluble form, targeting the delivery of ACPs, non-systemic side effects and specific treatment efficacy (138). Numerous natural peptides derived from natural products, such as bioactive peptides, are applied in cancer therapy (139).

Although naturally bioactive peptides exhibited beneficial biocompatibility and low cytotoxicity, a number of bioactive peptides cannot provide the active targeting, cell uptake, cancer cell cytotoxicity and targeted delivery (140). The natural active peptides can be modified to novel peptides with special properties, including specificity, higher cell penetration, cancer cell cytotoxicity and therapeutic efficacy with no side effect. The present review focused on the therapeutic peptide development from natural peptides to modified peptides and targeting peptides for increasing the specific cancer cell targets.

Natural peptides. Anticancer peptides have been discovered and modified from antimicrobial peptides, and these resources produce natural peptides from various organisms, such as marine, plant, yeast, fungi, bacteria and bovine (141,142). Antimicrobial and anticancer peptides, especially cationic peptides, can kill both bacteria and cancer cells due to the similar negative net charge on their membranes (143). Proteins from nutrients can release bioactive peptides via enzymatic hydrolysis, gastrointestinal digestion or during fermentation (144). Bioactive peptides discovered from natural peptides have an electrostatic interaction between the peptides and cell membrane, leading to cancer cell or mitochondrial membrane disruption and then necrosis or apoptosis (145). For example, bioactive milk-derived peptides released during digestion have a vital role in cancer prevention (146). Moreover, germinated soybean protein-derived peptides from enzymatic hydrolysis exert antiproliferative activity against human colorectal cancer cells (147). It has also been shown that the extracted peptides from *Lentinus squarrosulus* mushrooms can mediate human lung cancer cells via apoptosis (148). Cyclic peptides isolated from marine cyanobacteria, such as *Urumamide*, exhibited low proliferative inhibitory activity on human cancer cells (149). Additional examples of natural peptides that have anticancer properties are presented in Table II and Fig. 3A. The majority of natural peptides that exert effects against cancer cell survival are α -helical folding peptides that have cationic properties (150,151). However, a minority of peptides, including other folding with neutral or anionic peptides, are able to disrupt cancer cell survival (152). Recently, a number of anionic antimicrobial peptides that originate from amphibians, including frogs, toads, newts and salamanders across Africa, South America and China, demonstrated anticancer activity (153). Thus, natural ACPs can exhibit both cationic and anionic or neutral properties; also, the majority of cationic peptides are found to have a significant cytotoxic effect against cancer cells compared with anionic or neutral peptides. In the future, these natural ACPs can be modified to further ACP development.

Modified peptides. Highly cationic and amphipathic peptide properties can be synthesized and designed via *in silico* creations. For example, some chemical groups, such as acetylation or amidation, are added into the natural peptides to increase the cationic properties and target cell specificity (162). Replacement of D-amino acids in an amphipathic peptide, KLALKLALKALKAAKLA-NH₂, and a hydrophobic interaction can increase the membrane-disrupting effect on high negative surface charge bilayers, which then promotes peptide penetration into the inner membrane regions (163). Moreover, the folding and formation of peptides, such as the α -helix or cyclization, results

in an increase in anticancer properties and stability (164,165). It has also been revealed that fewer helical peptides can decrease the bilayer disruption activity (163), and that cyclic peptides can act on cell permeability (45). Furthermore, substitution, deletion or addition of positively charged or polar and non-polar amino acids on natural peptides could modify their properties to improve therapeutic application (164,165). Some modified peptides are displayed in Table III and Fig. 3B.

Besides the aforementioned modifications, ACPs have been constructed via genetic engineering, including anticancer fusion peptides; for example, the structure of bovine lactoferricin and hexapeptide derived from bovine milk protein for ovarian cancer treatment (166). NT4 peptides bound to GAG chains of heparan sulfate proteoglycans have a modulatory effect on the cancer cell migration and invasion ability (167). A recombinant protein consisting of iRGD (CRGDKGPDC)-conjugated KLA peptide (KLAKLAKKLAKLAK) exerts a pro-apoptotic activity and high penetration to tumor tissue and cells for gastric cancer treatment (40). Collectively, modified peptides can be developed to improve anticancer properties and the effect on the cancer targets directly.

Targeting peptides. The discovery of cancer cell targets can promote cell target specificity to avoid healthy cell damage (172). Targeting peptides on various cancer cell types should bind to cancer cell targets and eliminate cancer cells at the same time (173). Molecular targets in cancer cells are important for clinical therapy, including vascular endothelial growth factor, RAS/mitogen-activated protein kinase pathway inhibitors, aurora kinase inhibitors or endothelin receptor antagonists (174,175). Some molecular targets can induce an immune response, such as cytokines, while others directly bind to specific cancer cell biomarkers (175,176). Upregulation of specific cancer proteins or peptides has been used as cancer targets (139). For instance, high expression levels of MDM2 proto-oncogene (MDM2) and MDM4 regulator of p53 (MDMX), as negative regulators of tumor suppressor protein p53, and upregulated expression of the cell surface receptor CD33 have been targeted for AML therapy (177). Lanthanide oxyfluoride nanoparticle (LONp) bound dual-specific peptide antagonists of MDM2 and MDMX (PMI) and antiCD33-LONp-PMI can activate the p53 pathway, thus inducing AML cell apoptosis (177). Furthermore, upregulated urokinase plasminogen activator receptors (uPAR) on cancer cells are targeted to uptake a specific peptide, 68Ga-labeled AE105 peptide, as uPAR PET-probes, into U87MG tumor cells (178). Examples of the targeting peptides are presented in Table IV and Fig. 3C. Besides disturbing cancer cell survival, targeting peptides for cancer cell labeling was an advantage for cancer cell detection and diagnosis. For example, 99mTc-(tricine)-HYNIC-Lys-FROP peptides were taken up by breast cancer cells for tumor targeting and molecular imaging (179). Therefore, targeting peptides can specifically and directly bind and destroy cancer cells, but not healthy cells. However, their targets are difficult to discover and develop for specific cancer cell therapy.

4. Anticancer peptides in clinical trials

Several synthetic peptide-based drugs and vaccines are currently undergoing clinical trials. The National Library

Table II. Examples of natural peptides against cancer cells.

Source	Name	Sequence	Net charge ^a	Structure ^b	Against cancer cell types	Biological mechanism (Refs.)
<i>Buthus Occitanus tunetanus</i>	RK1	IDCSKVNLTAECS	-1	α -helix	IGR39, U87 cells	Reduce cell proliferation and migration (154)
Cancer stem-like cells	EpCAM peptide-CTLs	VVAGIVVLV GLKAGVIAV VLAFGLLLA RTYWIIIEL SMCWCVNTA SMQGLKAGV ILYENNVIT LLLLAAATAT	0 +1 0 0 0 +1 -1 0	Extend Coil α -helix Extend Extend/coil α -helix/coil Coil α -helix	EpCAM-expressing HepG2 cells	Inhibit tumor growth and induce specific immune response (155)
Cancer stem-like cells	CD44 peptide-specific CTLs	YIFYTFSTV LILAVCIAV SLALALIL IILASLLAL WLILASLL VLLQTTTRM GLVEDLDRT TVGDSNSNV TFDYLRSLV	0 0 0 0 0 +1 -2 -1 0	Extend α -helix α -helix α -helix α -helix Coil/extend α -helix/coil Coil α -helix	CD44 positive MCF-7 tumor cells	Kill tumor cells (155)
Tyrosine-protein kinase Lck	Lck-486 peptide		0	α -helix	Some metastatic tumor cells and T-cells at the tumor site	Inhibit tumor cell growth (156)
<i>Bombina orientalis</i>	Bombinin-BO1	GIGSAILSAGKSIKGLAKGLAEHF	+2	α -helix/coil	Human hepatoma cell lines (Hep G2, SK-HEP-1 and Huh7)	Anti-proliferative effects (157)
<i>Bombina orientalis</i>	Bombinin H-BO1	IIGPVLGLVGKALGGLL	+1	α -helix/coil	Human hepatoma cell lines (Hep G2, SK-HEP-1 and Huh7)	Anti-proliferative effects (157)
<i>Ichthyophthirius multifiliis</i> (strain G5) (White spot disease agent) (Ich)	BP100	KKLFKKILKYL	+5	α -helix	K562 cells	Promote LDH release (41)
A specific Eps8/EGFR inhibitor	Peptide 327	EFLDCFQKF	-1	α -helix	HT-29 cells	Immune response to tumor cell recognition (158)
<i>Anthopleura anjunae</i> (sea anemone)	<i>Anthopleura anjunae</i> anti-tumor peptide (AAP-H)	YVPGP	0	Coil	Prostate cancer DU-145 cells	Increase apoptosis via pro-apoptotic proteins (159)

^aPredicted using PepDraw (<http://www.tulane.edu/~biochem/WW/PepDraw/index.html>). ^bPredicted using PEP-FOLD 3.5 (144,145). BO, *Bombina orientalis*; CTLs, Cytotoxic T lymphocytes; EpCAM, Epithelial cellular adhesion molecule.

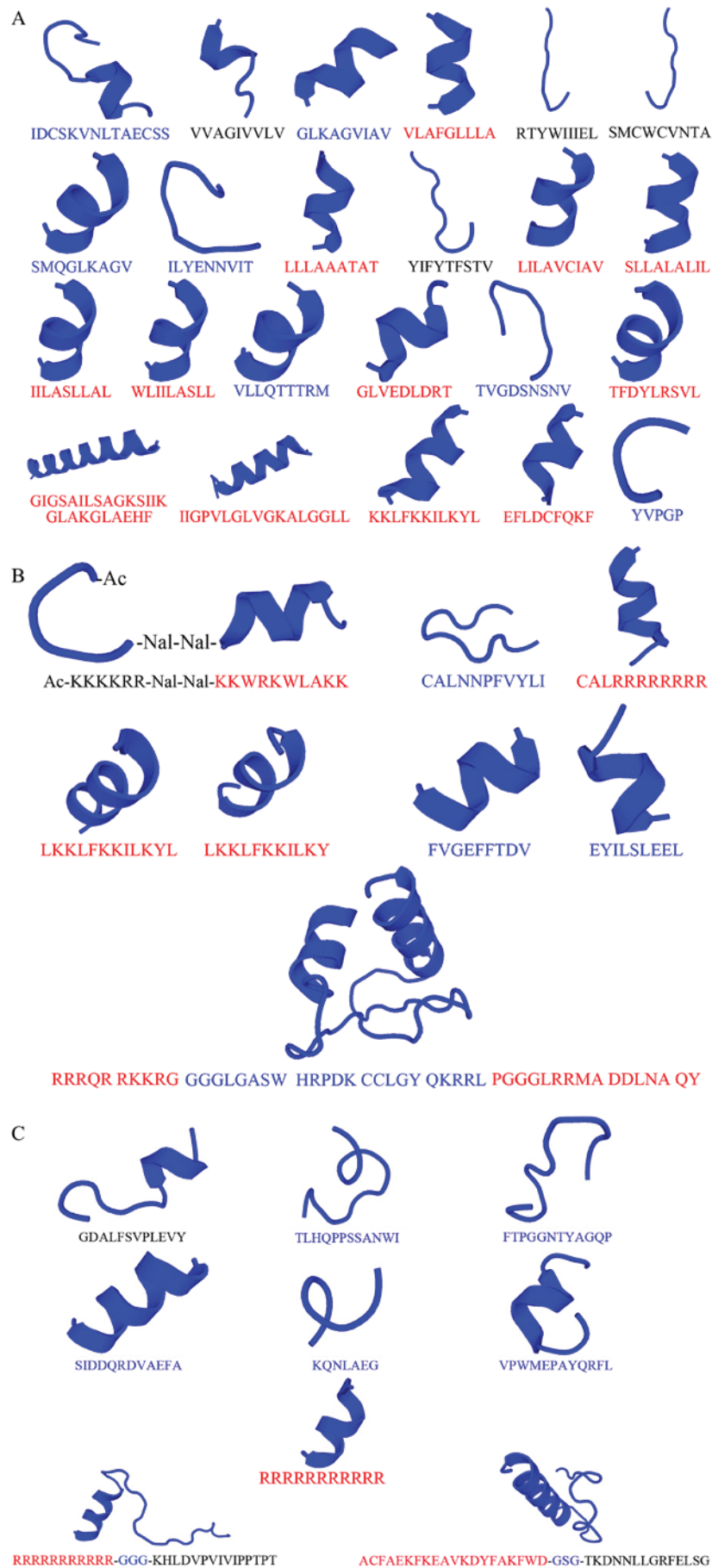


Figure 3. Conformation of anticancer peptides predicted using PEP-FOLD 3.5 (<https://mobile.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py#forms::PEP-FOLD3>). (A) Natural, (B) modified and (C) targeting peptides corresponding to Tables II-IV, respectively, performed in three conformations including extend (black alphabet amino acid sequences), coiled (blue alphabet amino acid sequences) and α -helix (red alphabet amino acid sequences).

Table III. Examples of modified peptides against cancer cells.

Source	Name	Sequence	Property	Structure	Against cancer cell types	(Refs.)
S1 (Ac-KKWRKWLAKK-NH2)	Nal2-S1	Ac-Nal-Nal-KKWRKWLAKK-NH2	Cationic peptides	Amphipathic α -helical peptides	OECM-1, C9, SAS, A549, PC9, PC9-G	(168)
	K4R2-Nal2-S1	Ac-KKKRRR-Nal-Nal-KKWRKWLAKK-NH2				
	K6-Nal2-S1	Ac-KKKKKK-Nal-Nal-KKWRKWLAKK-NH2				
<i>Drosophila Antennapedia homodomain</i>	PFV	CALNNPFVYLI	Neutral ^a	Coil/extend ^b	B16, A549	(169)
	R8	CALRRRRRRRR	Cationic peptides ^a	α -helical peptides ^b		
<i>Ichthyophthirius multifiliis</i> (strain G5) (White spot disease agent) (Ich)	B4	LKKLFKKILKYL	Cationic peptides ^a	α -helical peptides	K562	(41)
	B8	LKKLFKKILKY				
	GPC3(144-152)	FVGEFTDV	Anionic peptides ^a	Coil/ α -helical peptides ^b	The HLA-A 02:01 human cancer cell lines, HepG2, Wilm's tumor	(170)
Carcinoembryonic antigen glypican-3	GPC3(298-306)	EYILSLEEL			G-401, SK-N-DZ, HuH-6	
					MDAMB-231 and MCF-7	(171)
Transactivator of transcript-DV1-Bcl-2 homology 3	TAT-DV1-BH3 polypeptide	RRRQR RKKRG GGGGLGASW HRPDK CCLGY QKRRRL PGGGLRRMA DDLNA QY	Cationic peptide ^a	α -helical-coil- α -helical peptide ^b		

^aPredicted using PepDraw (<http://www.tulane.edu/~biochem/WW/PepDraw/index.html>). ^bPredicted using PEP-FOLD 3.5 (160,161). Nal, β -naphthylalanine; Ac, Acyl group; GPC, glypican; BH3, Bcl-2 homology 3.

of Medicine (NLM) at the National Institutes of Health (NIH) provides and updates clinical trial information on the ClinicalTrials.gov website. A total of 792 studies between 1995-2019 were identified and searched for 'cancer', 'peptide', 'drug' or 'biological' key words, excluding non-anti-cancer peptide interventions such as behavior and surgery. The search result is presented in Fig. 4.

For example, CIGB-300, an amidated disulfide cyclic undecapeptide fused to the TAT cell-penetrating peptide via a β -alanine spacer, inhibits CK-2-mediated phosphorylation leading to cancer cell apoptosis in patients with cervical and non-small cell lung cancer (185-187). Wilms' tumor 1 (WT1) peptide-based vaccination combined with the adjuvant drug OK-432 administered to pediatric patients with a solid tumor has been demonstrated to be safe for these children (188). Furthermore, WT1-pulsed dendritic cell vaccine has been used to treat patients with surgically resected pancreatic cancer under a phase I study (189). A modified 9-mer WT1 peptide vaccine was also used in patients with gynecological cancer for inducing myeloid dendritic cells, and was demonstrated to be associated with cytotoxic T-cell activation (190). Subsequently, WT1 peptide vaccine therapy was evaluated in patients with gynecological cancer in a phase II clinical trial (191). A target of esophageal squamous cell carcinoma and lung cancer types is lymphocyte antigen 6 complex locus K (LY6K), which is expressed in gastric cancer (192). LY6K-177 peptide vaccine emulsified with Montanide ISA 51 was evaluated in patients with gastric cancer as a phase I clinical trial, and was found to be tolerated by patients with advanced gastric cancer (50% of patients with gastric cancer had stable disease and 16% patients had a tumor contraction effect) (192).

B-cell lymphocytic leukemia and pancreatic cancer have demonstrated a high level of telomerase activity (193). GV1001, a peptide based-cancer vaccine derived from the hTERT (hTERT 616-626; EARPALLTSRLRFIPK), was administered in patients with non-resectable pancreatic cancer undergoing a dose-escalating phase I/II study (194); GV1001 was capable of inducing CD4⁺ and CD8⁺ T-cells, interacting with professional antigen-presenting cells and then engulfing dead tumor tissue or cells (194). Moreover, GV1001 may be a candidate vaccine in patients with B-cell chronic lymphocytic leukemia that exhibit telomerase-specific leukemic cells (195).

A combination of the ACPs and other drugs have also been evaluated in phase I trials, such as cyclodepsipeptide plitidepsin and bevacizumab in refractory solid tumors (196). For the binding peptide strategy, a carrier peptide, as a luteinizing hormone-releasing hormone (LHRH) agonist, is linked to the cytotoxic analogs of LHRH for cancer expressing receptors for LHRH (197). The LHRH agonist under phase II clinical trial exhibits anticancer activity in LHRH receptor-positive cancer types, such as human endometrial, ovarian and prostate cancer (197). Previously, a personalized peptide vaccination (PPV) has been developed as a novel approach for a cancer vaccine to boost the immune response using specific peptides for each patient (198). The peptides for PPV treatment under a randomized phase II trial in patients with bladder cancer were selected from the candidate peptides, according to human leukocyte antigen types and peptide-reactive IgG titers, to observe progression-free survival, overall survival, immune

Table IV. Examples of targeting peptides bind to specific cancer cells.

Name	Sequence	Net charge ^a	Structure ^b	Targeting cancer cell types	(Refs.)
CSP-GD	GDALFSVPLEVY	-2	Extend/coil	Human cervical cancer	(139)
CSP-TL	TLHQPPSSANWI	0	Coil	derived cells (SiH)	
CSP-FT	FTPGGNTYAGQP	0	Coil		
CSP-SI	SIDDQRDVAEFA	-3	Coil/ α -helix	Human cervical cancer	(139)
CSP-KQ	KQNLAEG	0	Coil/ α -helix	derived cells (C-33A)	
p160	VPWMEPAYQRFL	0	Coil/ α -helix	Neuroblastoma and breast cancer cell lines	(180,181)
Polyarginine (R11)	RRRRRRRRRRR	+11	α -helix	Bladder cancer	(182)
DN-C16orf74	RRRRRRRRRRR-GGG-KHLD VPVIVIPPTT	+11	α -helix-coil-extend	Pancreatic cancer cells	(183)
α -helix HSP70 peptide	ACFAEKFKAEVVDYFAKFW- GSG-TKDNLLGRFELSG	0	α -helix-coil-extend	Tumor regression on mice B16OVA melanoma models	(184)

^aPredicted using PepDraw (<http://www.tulane.edu/~biochem/WW/PepDraw/index.html>). ^bPredicted using PEP-FOLD 3.5 (160,161). CSP, cancer-specific targeting peptide; HSP, heat shock protein.

response and toxicity (198). Similarly, 19 mixed peptides were selected from 31 PPVs according to the anti-tumor immunological effect, and the safety profiles for patients with metastatic breast cancer were also assessed in a phase II clinical trial (199). While some peptides, such as gp100:209-217 (210M)/Montanide™ ISA-51/Imiquimod for high risk melanoma and E39 peptide/GM-CSF vaccine plus E39 booster for ovarian cancer, have been approved by the Food and Drug Administration (FDA), these have been improved in clinical therapy, such as peptide boronate bortezomib (200-202). The peptide boronate bortezomib is a reversible 26S proteasome inhibitor, degenerating several intracellular proteins, with antitumor and antiproliferative activities and can be used in multiple myeloma therapy (202). Due to adverse effects, such as hematotoxicity and peripheral neuropathy, poor penetration into solid tumors and low clinical stability and bioavailability, bortezomib was developed for delivery using nanoparticles, and treatment for bortezomib resistant multiple myeloma was improved using target chemical modification during synthetic processes (203,204). Additional ACP examples are presented in Table V. As aforementioned, various cancer vaccines have been produced using ACPs and ACPs combined with adjuvants or drugs, and the effects of carrier peptides on targeting cancer cell directly and/or by activating immune response have been tested in clinical trials for safety, side effects and effectiveness.

5. Future direction

Although ACPs have a number of disadvantages, such as biological instability, low bioavailability, short half-life, protease sensitivity, poor pharmacokinetics and first-pass metabolism, their most notable advantage is the protein-protein interaction with a target, thus overcoming limitations via designing peptide modifications and conjugation to improve affinity, stability and selectivity (205,206). For example, the peptide BBN₇₋₁₄ (Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂)

composed of natural amino acids has a higher binding affinity with the CFPAC-1 cell line compared with the modified peptide GB-6 (Gln-5-Htp- β -Ala-Nva-Gln-His-NH₂) that consists of unnatural amino acids (*in vitro*). However, *in vivo*, BBN₇₋₁₄ has a reduced tumor-targeting ability compared with GB-6, which is stable against protease-mediate degradation and has a slightly lower uptake and slow metabolism (207). Currently, ACPs have been modified to improve specific cancer cell targets and enhance cancer cell elimination. Some anticancer peptides as drugs and vaccinations have been tested in phase I/II clinical trials (175). For example, dTCAPFs, a natural hormone peptide for the treatment of advanced or metastatic solid tumors, enters the cells via the Toll/interleukin-1 receptor superfamily, suppresses angiogenic factors and induces anticancer cytokine production and ER stress, leading to cancer cell apoptosis (208). dTCAPFs anticancer activity in humans was firstly studied in a phase I clinical trial by investigating the safety and efficacy with regards to both pharmacokinetics and pharmacodynamics, with intravenous dTCAPFs (6-96 mg/m²; 3 times/week; in consecutive 28-day cycles) (209). The intravenous dTCAPFs is decreased at lower limit of detection in serum after 24-h administration and its concentration in serum is present in dose-dependent manner (209). Furthermore, ACPs have been combined with immunogens for clinical therapeutic improvement (210). Upregulation of molecular cancer targets, such as Ras protein that has been discovered in various cancer cell types (lung, colon and pancreatic), could also be direct targets for ACP development (211). The aim of ACP therapy should promote cancer cell death and intermit tumor regression, without contributing to tumorigenesis and resistance in cancer cell treatment (212). The first ACP approved by the FDA was the peptide boronate bortezomib (Velcade®) for multiple myeloma treatment in 2003 and mantle cell lymphoma in 2006 (213). In the near future, combination therapy with a drug or vaccine containing i) the specific targeting peptides, ii) the ACPs and

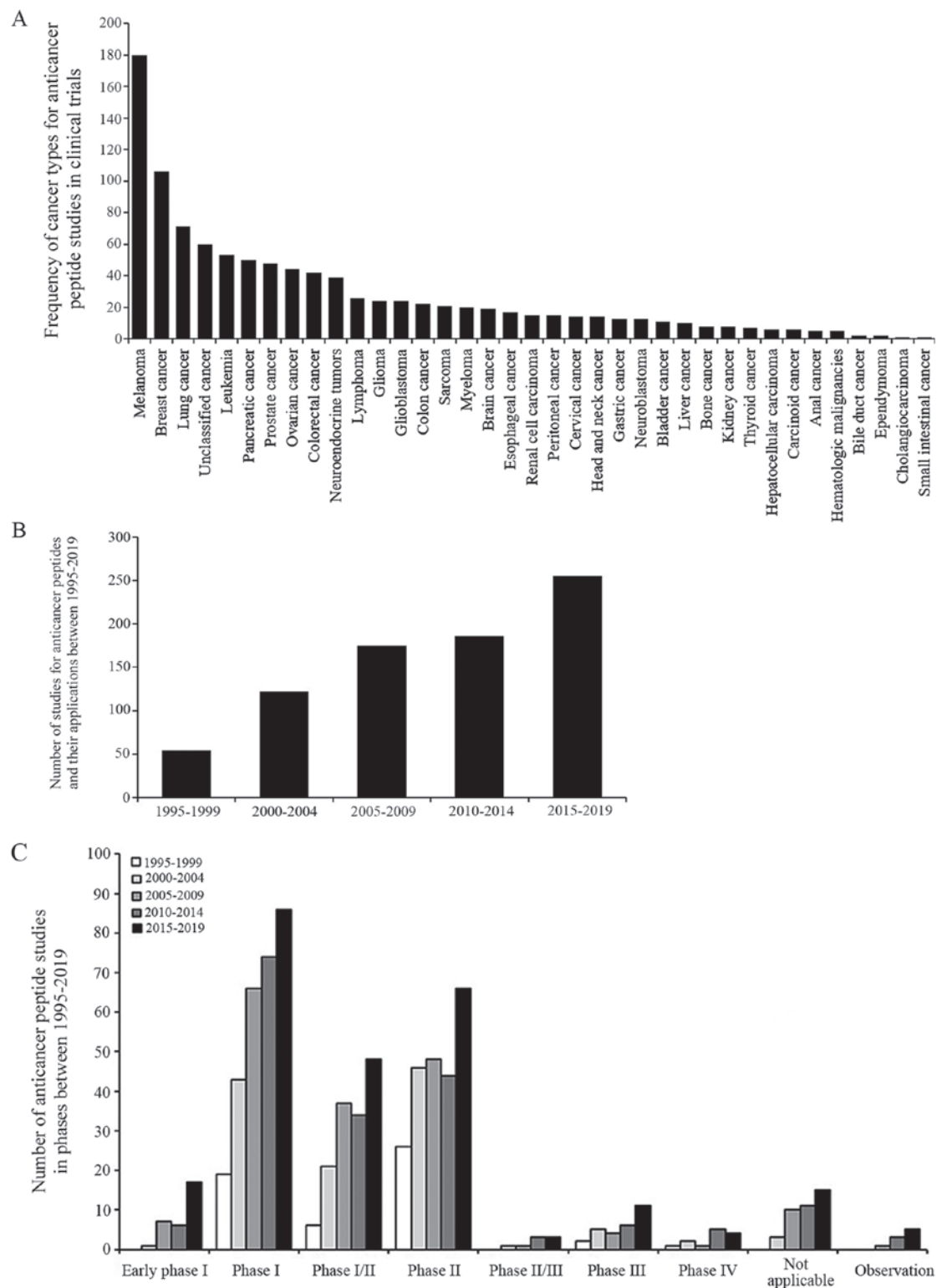


Figure 4. Number of ACP studies for the drug and biological intervention. (A) Frequency of cancer types from 792 ACP studies, which were submitted on the ClinicalTrials.gov website, including 36 cancer types and unclassified cancer types. The unclassified cancer types were reported as solid tumors, cancer or neoplasms. (B) Number of ACP studies in every 5-year period between 1995-2019 was continuously increased. (C) Furthermore, from 1995-2019, >98% of these ACP studies were an intervention study type, including clinical trial in early phase I, phase I, I/II, II, II/III, III, IV and not applicable, while <2% of them were an observation study type, which cannot assign a specific intervention or treatment. Source: www.clinicaltrials.gov search on Feb 4, 2020 with drug, biological and peptide key words in cancer. ACP, anticancer peptide.

iii) the cell-penetrating peptides and/or the conjugated delivery materials (such as liposome, nanoparticles or adjuvants) may facilitate the development of cancer therapy with cancer cell specificity, stability, safety and efficacy, without healthy

cell eradication (214). ACP construction for specific cancer cell targets, and predictive, preventive and personalized medicine may be beneficial to the cancer research field due to the different complexity of the whole-body system in each individual (215).

Table V. Examples of ACPs in clinical trials (source: www.ClinicalTrials.gov).

Phases	Biological peptides	Conditions	Outcomes
Early phase 1	MUC-1 peptide vaccine, poly ICLC, Breast cancer MUC1 peptide-poly-ICLC adjuvant vaccine HER-2/neu peptide vaccine	Breast cancer	A positive anti-MUC1 antibody response Peptide-specific interferon- γ producing T-cell and peptide-specific IL-5 producing T-cell responses
	GAA/TT-peptide vaccine and poly-ICLC Peptide vaccine + poly-ICLC	Astrocytoma, oligoastrocytoma, glioma Astrocytoma, oligoastrocytoma, oligodendroglioma	Induction of GAA-specific T-cell response Infiltration of GAA-specific T-cells
Phase 1	Gag:267-274 peptide vaccine HPV16 E7 peptide-pulsed autologous DCs NY-ESO-1b peptide plus CpG 7909 and Montanide ISA-5 Antiangiogenic peptide vaccine RNF43-721 LY6K, VEGFR1, VEGFR2	Melanoma Cervical cancer Cancer, neoplasm Hepatocellular carcinoma Colorectal cancer Esophageal cancer	Vaccine peptide-specific CTL response Pulsed autologous DCs immunotherapy NY-ESO-1 specific humoral and cellular immunity Peptide specific CTL response Specific CTL induction <i>in vitro</i> Immune responses including LY6K, VEGFR1 and VEGFR2 specific T-cells
	HLA-A*0201 or HLA-A*0206-restricted URLC10 peptides	Non-small cell lung cancer	Immunological responses including peptides specific CTL, antigen cascade, regulatory T-cells, cancer antigens and HLA levels.
Phase 1/Phase 2	MAGE-3.A1 peptide and CpG 7909 VEGFR1-1084, VEGFR2-169 HER-2/neu peptide vaccine HLA-A*2402 or A*0201 restricted peptides	Malignant melanoma Pancreatic cancer Breast cancer Solid tumors	Detectable CTL response Peptide specific CTL response HER2-specific T-cell response Various immunological responses including peptides specific CTL, antigen cascade, regulatory T-cells, cancer antigens and HLA levels
	Modified CEA peptide	Pancreatic adenocarcinoma	T-cell response with modified CEA peptide
Phase 2	synthetic human papillomavirus 16 E6 peptide gp100:209-217(210M), HPV 16 E7:12-20 WT1 126-134 peptide G250 peptide Melanoma helper peptide vaccine, multi-epitope melanoma peptide vaccine	Cervical cancer Melanoma Acute myeloid leukemia Metastatic renal cell carcinoma Melanoma	Immunological response to HPV T-cell immunity to gp100 peptide and to E7 12-20 papilloma virus peptide Generation of T-cell response G250-specific CTL response CTL response, helper T-cells response to 6MHP
Phase 3	PR1 leukemia peptide vaccine	Leukemia	Immune response to PR1-HLA-A2 tetramer
Phase 4	Degarelix (LHRH antagonist)	Prostatic neoplasms	Binds to GnRH receptors and blocks interaction with GnRH

From ClinicalTrials.gov searched on January 31, 2020. CTL, cytotoxic T-cell lymphocytes; GnRH, gonadotropin-releasing hormone; CEA, carcinoembryonic antigen; HPV, human papillomavirus; HER, human epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; MAGE-3, melanoma-associated antigen 3; RNF, ring finger protein; NY-ESO, New York esophageal squamous cell carcinoma; MUC, mucin.

Besides the aforementioned therapeutic peptides, peptides with specific cancer cell targets are applied to bind the cancer cell targets for cancer detection and therapy (216,217). For example, a sodium pump Na^+/K^+ ATPase $\alpha 1$ -targeted peptide

for positron emission tomography imaging of breast cancer, as peptide-based platform on dual-targeted molecular imaging, is able to more obviously visualize the disease state of a patient, leading to improved informed treatment decisions (218,219).

6. Conclusions

ACP therapy affects molecular targets, binds the anticancer drugs and stimulates biological systems involving cancer and healthy cell environments. Notably, natural and synthetic peptides have been developed as novel strategies against cancer types. Natural anticancer peptides can be modified to enable high penetration, specific cancer cell targets, increase efficacy and reduce side effects. A number of ACPs have been demonstrated to be anti-proliferative, apoptotic and proliferation inhibitors in various cancer cell types, both *in vitro* and *in vivo*, leading to clinical trials for the evaluation of cancer treatment. The development of drug or vaccine technology could further ACPs in design, synthesis and delivery to eliminate cancer cells directly or by affecting the anticancer immune responses (220). Collectively, it was suggested ACPs may promote cancer drugs or vaccine development to decrease emerging cases and mortality rates in the future.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WC wrote and edited the manuscript and was involved in the creation of the figures and data analysis. All authors were involved in the drafting and revising of the manuscript. All authors read the manuscript and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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