International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Cancer Chemotherapy with Peptides and Peptidomimetics Drug and Peptide Based-Vaccines

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Abstract— *A summary of the current status of the application of peptidomimetics in cancer therapeutics as an alternative to peptide drugs is provided. Only compounds that are used in therapy or at least under clinical trials are discussed, using inhibitors of farnesyltransferase, proteasome and matrix metalloproteinases as examples. The design and synthesis of peptidomimetics are most important because of the dominant position peptide and protein-protein interactions play in molecular recognition and signalling, especially in living systems. The design of peptidomimetics can be viewed from several different perspectives and peptidomimetics can be categorized in a number of different ways. Study of the vast literature would suggest that medicinal and organic chemists, who deal with peptide mimics, utilize these methods in many different ways. Conventional methods used to treat cancer, from non-specific chemotherapy to modern molecularly targeted drugs have generated limited results due to the complexity of the disease as well as lack of molecular classes that can be developed into treatments rapidly, easily and economically. Peptidomimetics that are easy to synthesize and optimize and has been studied in different oncology applications as great biologically amenable compounds and can be considered as a promising alternative molecular class for anticancer drug developments. Peptide can be utilized directly as a cytotoxic agent through various mechanisms or can act as a carrier of cytotoxic agents and radioisotopes by specifically targeting cancer cells. Peptide-based hormonal therapy has been extensively studied and utilized for the treatment of breast and prostate cancers. Tremendous amount of clinical data is currently available attesting to the efficiency of peptide-based cancer vaccines.*

Keywords— *Farnesyltransferase inhibitors, Ras, Metal-loproteinase inhibitors, Angiogenesis, Proteasome inhibitors*.

I. INTRODUCTION

Mortality from cancer is about to surpass that from cardiovascular diseases in near future. About 7 million people die from cancer-related cases per year, and it is estimated that there will be more than 16 million new cancer cases every year by 2020 [1, 2]. 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) [3]. Though angiogenesis (growth of new blood vessels from pre-existing vessels) is a normal and vital process in growth and development, it is also a fundamental step in the transition of b tumors from adormant state to a malignant one [4]. Chemotherapy is one of the major approaches to treat cancer by delivering a cytotoxic agent to the cancer cells. The main problem with the conventional chemotherapy is the inability to deliver the correct amount of drug directly to cancer cells without affecting normal cells [5]. Drug resistance, altered bio distribution, biotransformation, and drug clearance are also common problems [5]. Targeted Mortality from cancer is about to surpass that from cardiovascular diseases in near future. About 7 million people die from cancer-related cases per year, and it is estimated that there will be more than 16 million new cancer cases every year by 2020 [1, 2]. 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) [3]. Though angiogenesis (growth of new blood vessels from pre-existing 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 [4]. The “biologics” treatment option against cancer includes the use of proteins, monoclonal antibodies, and peptides. The monoclonal antibodies (mAbs) and large protein ligands have two major limitations compared to peptides: poor delivery to tumors due to their large size and dose-limiting toxicity to the liver and bone marrow due to nonspecific uptake into the reticulo endothelial system. The use of such macromolecules has therefore been restricted to either vascular targets present on the luminal side of tumor vessel endothelium or hematological malignancies [6–11]. Peptides possess many advantages such as small size, ease of synthesis and modification, tumor penetrating ability, and good biocompatibility [12, 13]. Peptide degradation by proteolysis can be prevented by chemical modifications such as incorporation of D-amino acids or cyclization [14]. Over the years peptides have been evolved as promising therapeutic agents in the treatment of cancer, diabetes, and cardiovascular diseases, and application of peptides in a variety of other therapeutic areas is growing rapidly. Currently there are about

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60 approved peptide drugs in the market generating an annual sale of more than $13 billion [14]. Out of four peptide drugs in the market which have reached global sales over $1 billion, three peptides are used in treating cancer directly or in the treatment of episodes associated with certain tumors (leuprolide, goserelin, and octreotide). The number of peptide drugs entering clinical trials is increase ingsteadily; it was 1.2 per year in the 1970s, 4.6 per year in the 1980s, 9.7 per year in the 1990s, and 16.8 per in 2000s [15]. There are several hundred peptide candidates in the clinic and preclinic development. From 2000 onwards, peptides entering clinical study were most frequently for indications of cancer (18%) and metabolic disorders (17%) [16]. this paper focuses on diff erent strategies of employing peptides in cancer treatment and management. A special emphasis is given to current peptide drugs available in the market for treating cancer and also peptide candidates in clinical and preclinical stages of development. Peptides can be utilized in a number of different ways in treating cancer [17]. This includes using peptides directly as drugs (e.g., as angiogenesis inhibitors), tumor targeting agents that carry cytotoxic drugs and radionuclides (targeted chemotherapy and radiation therapy), hormones, and vaccines. Different possible cancer treatment options using peptides are summarized in Figure 1.

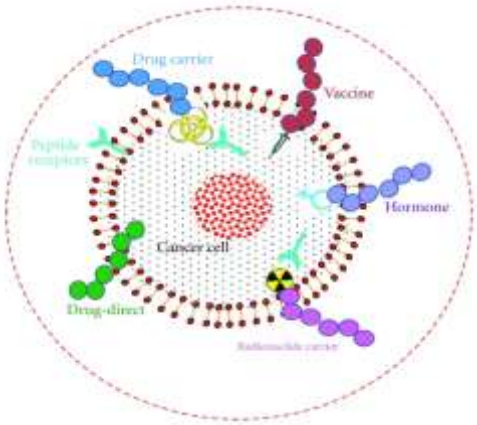

Fig. 1. Different possible treatment options of cancer using peptides. Peptides can be used as anticancer drug, cytotoxic drug carrier, vaccine, hormones, and radionuclide carrier.

Peptides & peptidomimetics:

The use of peptides as drugs began as early as the 1950s with the discovery of hormones and neurotransmitters and treatment with peptide-based drugs for hormonal therapy [23, 24]. Peptide-based drug design gained momentum as 3D structures of proteins and their functions on cell surfaces as well as in cells were delineated. Particularly for the immune response, several proteins are involved on cell surfaces that interact with one another (Figure 1), forming an immunological synapse [18, 19]. Structural and functional studies of the proteins have suggested that protein–protein interaction (PPI) is required for any cell signaling process. Protein–protein complexes are transient and reversible. In the immune response, these interactions are dynamic in nature and the signal depends on the strength and duration of interaction. The amino acids that are present on the surface of proteins provide them with high specificity and affinity yet dynamic binding character. Since PPI surfaces are made up of epitopes of amino acids, peptides are a relevant choice to modulate such interactions.

To overcome short half-life and low bioavailability, several strategies have been investigated that can be adopted in the design of peptide-based drugs [20]. In vivo stability of peptides can be enhanced by peptide backbone modification; this can be accomplished by introduction of unnatural amino acids or D-amino acids, peptide-bond modification, N-and C-termini modifications and constraining the backbone by introducing cyclization, resulting in molecules that are stable against enzymatic degradation [21-23]. Bioavailability and renal clearance problems can be overcome by PEGylation of the peptides. Modification of the backbone or side chain of peptides produces peptidomimetics. Peptidomimetics are compounds whose pharmacophore mimics a natural peptide or protein in 3D space with the ability to interact with the biological target and produce the same biological effect. The idea behind this design is that proteins exert their biological effects through small regions on their surface called epitopes. A short sequence of peptides or functional groups that are close together can be reproduced in smaller, conformationally similar fragments that can bind to the receptor and provide steric hindrance between the receptor and the native protein ligand. Peptidomimetics have advantages over peptides in terms of stability and bioavailability associated with a natural peptide. Therefore, peptidomimetics have great potential in drug discovery. Peptidomimetics can have main- or side-chain modifications of the parent peptide designed for biological function (Figure 2A–2D) [24-27]. Some examples of peptidomimetics structures that are therapeutically useful and that are already in the market for cardiovascular disorder are shown in Figure 2E. In terms of design considerations, peptidomimetics can be designed from protein epitopes with global or local conformational restrictions.

Global conformational restrictions impose a particular shape or secondary structure on the peptide and also provide stability against enzymatic degradation. Examples of global conformational constraints include cyclization of the peptide using non peptide moieties, lactam bridges or inclusion of penicillamine (dimethyl cysteine) to form disulfide bonds. Local conformational restrictions can be applied using backbone modifications at particular amino acid residues or between two amino acid residues in the peptide. Backbone amides can be replaced by amide bond-like surrogates and isosteric substituents (Figure 2B) [28]. These backbone-modified mimetics can have regular amino acids. Side chains of amino acids in the peptides can be replaced with analogs of amino acids that have functional properties similar to those of amino acid side chains but with conformational restrictions of χ angles for side-chain rotation (Figure 2C). The side chain-modified peptidomimetics can expose the proper functional groups to bind with the targeted receptors with high affinity compared with normal side chains of amino acids. Another tactic to design the peptidomimetics is a minimalistic approach [29] where the secondary structure of the peptide epitope is mimicked using α-helical, β-turn or β-strand

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constraints to introduce organic functional groups (Figure 2D). the peptide design strategy to multi cyclic structures of naturally occurring, enzymatically stable peptides or miniproteins.

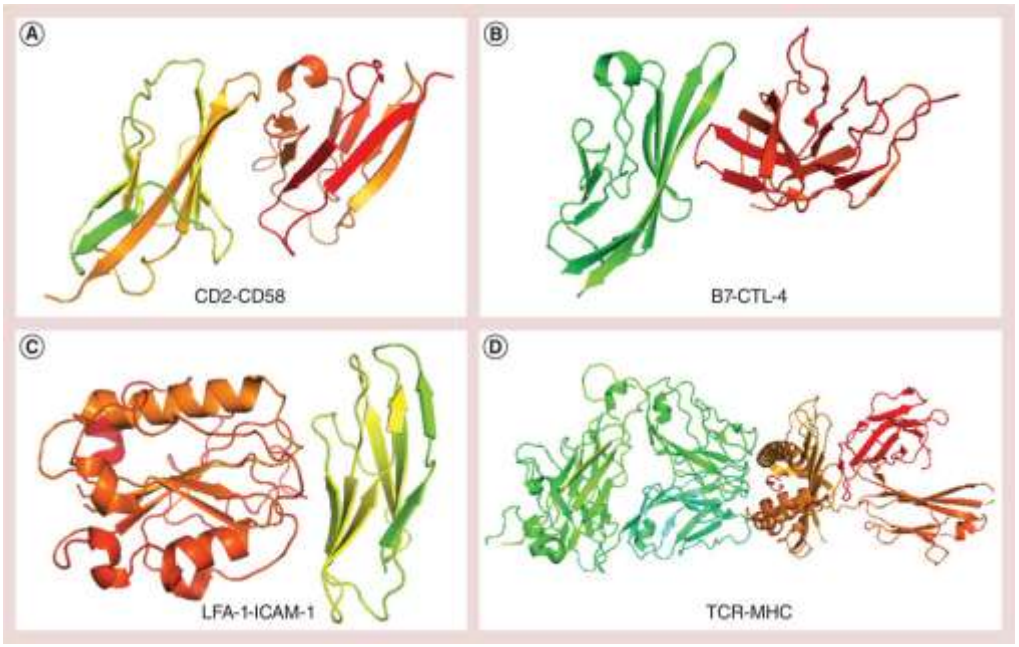

Fig. 2. Crystal structures of protein complexes that are involved in adhesion or co-stimulation during immune response. An array of these molecules on the T cell and antigen-presenting cell facilitates the contact between the cells apart from TCR-MHC molecules. (A) CD2-CD58 (Protein Data Bank ID: 1AQ9), (B) B7-CTL-4 (Protein Data Bank ID: 1I8L), (C) LFA-1-ICAM-1 (Protein Data Bank ID: 1MQ8) and (D) TCR-MHC (Protein Data Bank ID: 1G6R). CTL: Cytotoxic T lymphocyte; LFA: Leukocyte function-associated antigen; TCR: T-cell receptor.

Cancer

Immunotherapy has an advantage over radiation and chemotherapies in that it can act specifically against the tumor without damaging normal tissue. Most anticancer drugs have high toxicities or generate immune response and resistance, often resulting in relapse and metastasis [30–33]. The approach of immunomodulation in immunotherapy is a necessary new trend for cancer therapy. The idea is to train the immune system to recognize the tumor cells and kill them [34]. Antigen specific cancer immunotherapy can achieve this goal by targeting systemic tumors. Although preventive vaccination has been known for a long time, therapeutic vaccination has not progressed like targeted biologics such as antibodies. This approach requires induction of cell -mediated immunity that is capable of attacking and eliminating antigen-bearing cells. There has been some success in cancer therapy using therapeutic vaccines [35–37], but the use of peptides and peptidomimetics for immunotherapy of cancer is a novel method that is in progress. Immunization with antigenic peptides containing B- or T-cell epitopes or both B- and T-cell epitopes can stimulate a patient's own immune system to develop specific high-affinity antibodies. Once the antibodies are developed against a cancer antigen, the treatment can continue without frequent dosing of the peptide-based drugs. These peptides must be designed based on epitopes of antibodies or antigens [38]. The advantages of these peptide-based therapies are that they can be easily modified and, in most cases, they are nontoxic, do not develop resistance and are cost effective. Most of the development in this area is related to HER2-positive cancers or VEGF-related cancers [39–42]. Here, we briefly describe some of these approaches. In the case of known proteins that can be used as B- or T-cell epitopes, the design is based on the binding region of the antibody. In the case of an unknown protein, prediction of the epitope has to be carried out with the available data on antigenicity, hydrophilicity and secondary structure propensity (Figure 3).

These peptides, called 'm-peptides', can be designed as peptide vaccines. At present, these approaches are still being evaluated in animal models by different researchers [43, 44].

II. PEPTIDOMIMETICS IN CANCER CHEMOTHERAPY

A) Inhibitors of the Ras/Raf/MEK signalling pathway
B) Inhibitors of Ras processing by farnesyltranferase
C) Proteasome inhibitors
D) Antiangiogenic agents acting as metalloproteinase inhibitors

A) Inhibitors of the Ras/Raf/MEK signalling pathway:

The Ras proteins, the most important of which are HR as, K-Ras and N-Ras, belong to a large family of GTP-binding proteins (GTPases), and were among the first proteins identified as cell growth regulators. About 25% of human tumours, including nearly all pancreatic and at least 30% of colon, thyroid and lung cancers, have undergone an activating mutation in one of the Ras genes that leads to proteins remaining locked in an active state. Because of this large percentage of human tumours containing Ras mutants and their key role in maintaining the malignant phenotype,

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interruption of the Ras signalling pathway is an important focus of anticancer drug development [45-47] that has resulted in more than 20 new antitumour agents in clinical trials.

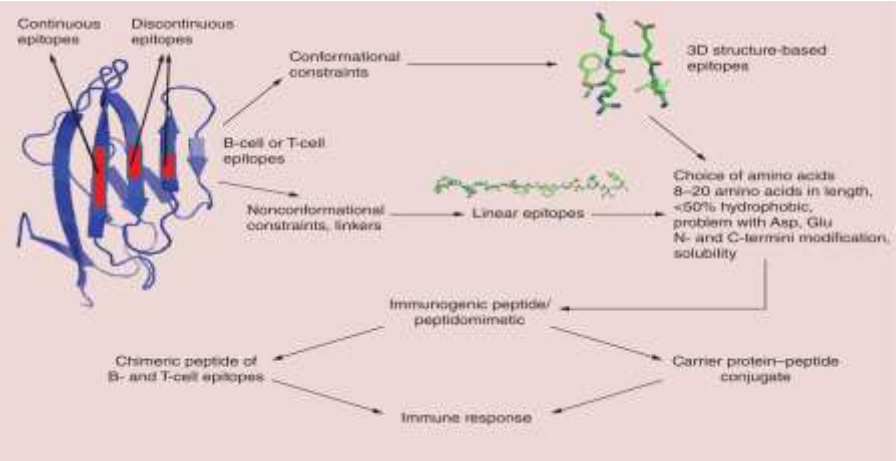

Fig. 3. Design of an immunogenic peptide. Linear or conformationally constrained peptides can be designed to generate an immune response for a particular antigenic sequence.

The Ras proteins need to be translocated to the membrane inner side in order to be able to recruit their target enzymes. Membrane-bound Ras cycles between the quiescent GDP-bound and the activated GTP-bound forms. This activation is triggered by alteration of the affinity of Ras for GDP, allowing exchange for GTP, by a multi protein scaffold formed by adaptor molecules such as Grb, which binds to phosphorylated tyrosine receptors to recruit effectors such as the so-called Son of Seven less (SOS). The active, membrane-bound Ras recruits the Raf family kinases, which in turn activate mitogen-activated protein kinase kinases (MEK) to phosphorylate mitogen-activated protein kinases (MAPK, also known as ERK) that then influence gene expression. While the above mechanism promotes GTP binding to Ras, a competing process that involves the so-called GTPase activating proteins (GAPs) prevents it by activating GTP hydrolysis ("Ras switch"). A single amino acid change at codons 12 (the most common in human cancer), 13 or 61 results in mutant Ras proteins that are not sensitive to control by GAPs and hence Ras is maintained in a GTP-bound ("on") state.

B) Inhibitors of Ras processing by farnesyltranferase

There are several approaches that have yielded clinically useful compounds acting at the Ras pathway, including the use of inhibitors of Ras protein expression, inhibitors of Ras processing by farnesyltranferase and inhibitors of downstream effectors of Ras function, but only the second type of inhibitors are relevant to the present summary. Newly synthesised Ras is a cytoplasmatic protein that requires a post-translational structural modification to render it sufficiently lipophilic to allow its anchoring in the membrane. This modification involves several steps (Figure 4).

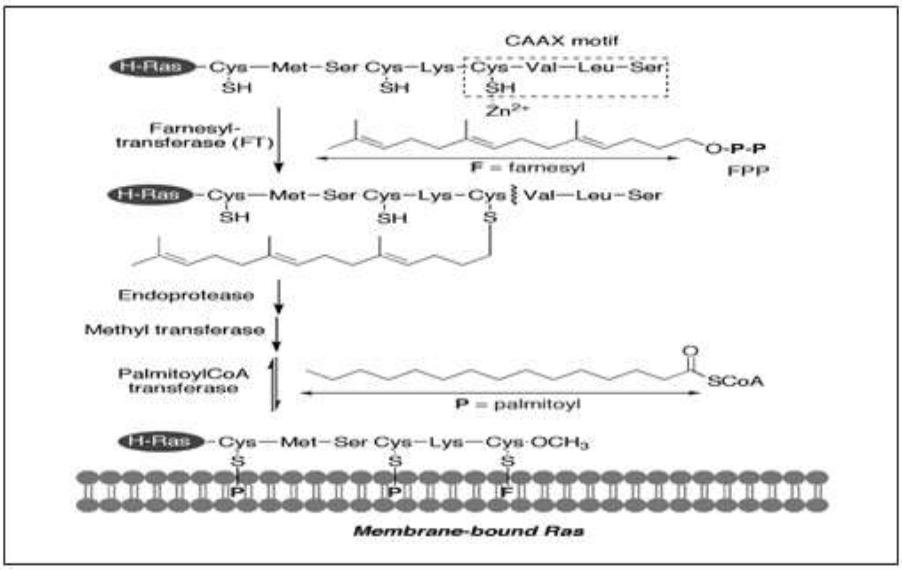

Fig. 4. Anchoring of Ras to the cell membrane.

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C) Proteasome inhibitors

Protein degradation is essential for the cell to supply fresh amino acids for protein synthesis and also to remove unneeded proteins, including excess enzymes and transcription factors that are no longer required or damaged. There are primarily two types of cellular structures that are in charge of protein degradation, namely lysosomes, which exert their proteolytic function on extracellular proteins from endocytosis and phagocytosis mechanisms and also on transmembrane proteins, and proteasomes, which act on damaged or unneeded endogenous proteins. The proteasome is an anticancer target [48] because it controls the levels of several proteins that are essential for the progression of the cell cycle and apoptosis, including cyclins, caspases, BCL2, the tumour-suppressing factor p53 and nuclear factor κB (NF-κB). Blocking the proteasome results in the accumulation of various other regulatory proteins, which leads to cell death by a variety of mechanisms. For instance, proteasome inhibition disrupts the regulation of the p53 tumour suppressor (which is mutated in about 50% of human cancers) by the murine double minute (MDM2) protein. This negative regulator exports p53 from the nucleus to the cytoplasm, and, because of its ubiquitin ligase activity, facilitates p53 destruction by the proteasome. For this reason, proteasome inhibitors may provide a good approach to the treatment of tumours that overexpress the MDM2 factor. These inhibitors may also act as anticancer agents by preventing the expression of pro-survival genes. Nucleophiles through their hydroxyl groups. In the case of epoxyketones, like the natural product epoxomycin, the X-ray crystal structure and spectrometric analysis of a complex between the inhibitor and the yeast Saccharomyces cerevisiae 20S proteasome showed the formation of the morphine derivative 5. The generation of this compound was explained by formation of hemiacetal 4 through reaction of the oxygen with the carbonyl group of the epoxyketone pharmacophore, followed by nucleophilic attack of the amino group onto the more hindered epoxide carbon atom with inversion of configuration [49].

D) Antiangiogenic agents acting as metalloproteinase inhibitors

In order for a tumour to grow beyond a size of about 2 mm3, it needs to develop a network of blood vessels (angiogenesis), a process that is regulated by pro-angio genic and anti-angiogenic factors. Angiogenesis processes are very important targets in cancer treatment [50, 51] but they cannot be fully discussed within the scope of this review. We will mention, however, a group of peptidomimetics that act as inhibitors of metalloproteinases, a class of proteolytic enzymes of the extracellular matrix (ECM). In response to angiogenic stimuli, endothelial proteases initiate the breakdown of the surrounding ECM, which allows the migration of proliferating endothelial cells and their growth to form lumens. Besides their role in cancer treatment [52], they are also being studied as targets for arthritis and emphysema due to their role in collagen degradation [53]. MMPs are also zinc-dependent proteolytic endopeptidases where the zinc cation is coordinated by three imidazole side chains from histidine residues, and a water molecule is the fourth ligand. All inhibitors replace this water molecule and coordinate to zinc in a monodentate or bidentate fashion. The mechanism for peptide hydrolysis by Zn-metalloproteinases is based on the enhanced acidity of the water molecule as a consequence of coordination of its oxygen atom with zinc (Figure 7). The design of the first generation of MMP inhibitors relied on the preparation of peptides and peptide-like compounds that combine backbone features that allow an interaction with enzyme subsites and functional groups capable of coordination with zinc. Among these, the hydroxamic acid group is a very potent 1, 4-bidentate Zn ligand that binds as an anion with two contacts to the cation and creates a distorted trigonal bipyramidal geometry around the metal [54].

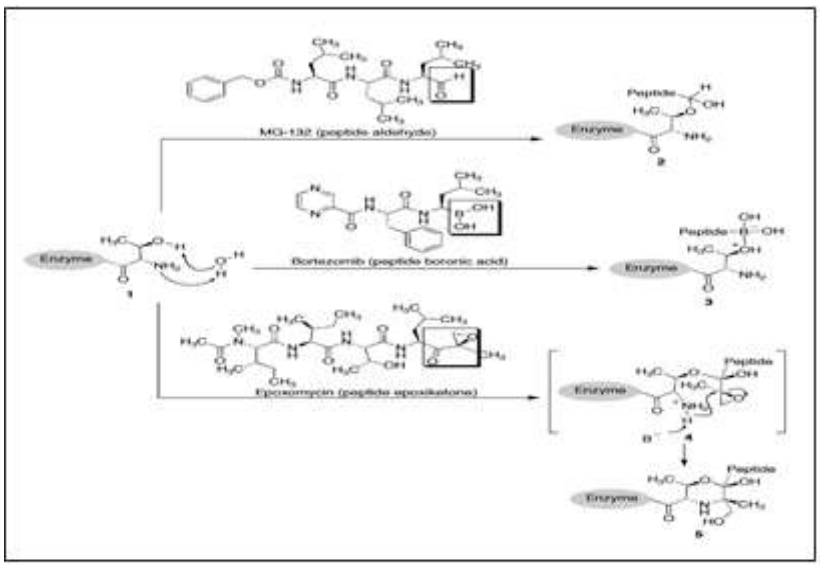

Fig. 7. Inhibitors of matrix metalloproteinases.

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Additionally, it also has a nitrogen atom for binding to the protein backbone. For this reason, peptide-like compounds that contain a hydroxamic acid portion are among the most potent known inhibitors of the MMPs, with potencies in the nM range. Among these first inhibitors, batimastat (BB-94) and marimastat are hydroxamic acid-based MMP inhibitors with little specificity.

Peptide Hormones: LHRH Agonists and Antagonists

The best classical example of the application of peptides in cancer treatment is the use of LHRH (luteinizing hormone releasing hormone) agonists introduced by Schally et al. as a therapy for prostate cancer [55–56]. Since then, depot formulations of LHRH agonists such as buserelin, leuprolide, goserelin, and triptorelin have been developed for more efficacious and more convenient treatment of patients with prostate cancer [57–59]. Administration of these peptides causes down regulation of LHRH receptors in the pituitary, leading to an inhibition of follicle-stimulating hormone (FSH) and LH release, and a concomitant decrease in testosterone production. This offered a new method for androgen deprivation therapy in prostate cancer patients. Discovery of LHRH antagonists resulted in therapeutic improvement over agonists as they cause an immediate and dose-related inhibition of LH and FSH by competitive blockade of the LHRH receptors. To date, many potent LHRH antagonists are available for the clinical use in patients. Cetrorelix was the first LHRH antagonist given marketing approval and, thus, became the first LHRH antagonist available clinically [60]. Subsequently new generation LHRH antagonists such as abarelix and degarelix have been approved for human use [61, 62]. A list of LHRH agonists and antagonists available in the market is shown in Table 1.

TABLE 1. LHRH agonists and new generation antagonists in the market.

Peptide	Sequence comparison	Indications
Agonists		
Buserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt	Prostate cancer
Gonadorelin	Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2	Cystic ovarian disease, agent for evaluating hypothalamic-pituitary gonadotropic function
Goserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH_2	Prostate cancer; breast cancer
Histrelin	Pyr-His-Trp-Ser-Tyr-D-His(N-benzyl)-Leu-Arg-Pro-NHEt	Prostate cancer; breast cancer
Leuprolide	Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt	Prostate cancer; breast cancer
Nafarelin	Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH_2	Treat symptoms of endometriosis, central precocious puberty
Triptorelin	Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2	Prostate cancer; breast cancer
Antagonists		
Abarelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3′-pyridyl) Ala-Ser-(N-Me)Tyr-D-Asn-Leu-isopropylLys-Pro-DAla-NH_2	Prostate cancer
Cetrorelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3′-pyridyl) Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2	Prostate cancer; breast cancer
Degarelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3′-pyridyl) Ala-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carbamoyl)-Leu-isopropylLys-Pro-D-Ala-NH_2	Prostate cancer
Ganirelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3′-pyridyl) Ala-Ser-Tyr-D-(N9, N10-diethyl)-homoArg-Leu-(N9, N10-diethyl)-homoArg-Pro-D-Ala-NH_2	Fertility treatment

Peptide as Radionuclide Carrier: Somatostatin Analogues in Cancer Therapy and Peptide Receptor Radionuclide Therapy (PRRT)

Apart from the use of peptide-based LHRH agonists and antagonists for treating cancer, somatostatin analogues are the only approved cancer therapeutic peptides in the market. Potent analogues of somatostatin (peptide hormone consisting of 14 amino acids, found in δ cells of the pancreas as well as in hypothalamic and other gastrointestinal cells) including octreotide (sandostatin) have been developed for the treatment of acromegaly, gigantism, thyrotropinoma, diarrhea and flushing episodes associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas)[63]. Peptide receptor radionuclide therapy (PRRT) combines octreotide (or other somatostatin analogs) with a radionuclide (a radioactive substance) to form highly specialized molecules called radiolabeled somatostatin analogues or radiopeptides [64]. 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 radio peptides can be injected into a patient and will trave lthroughout the body binding to carcinoid tumor cells that have receptors for them. Once bound, these radiopeptides emit radiation and kill the tumor cells they are bound to (Figure 8). PRRT using [111In-DTPA]-octreotide (where DTPA is diethylene triamine pentaacetic acid) is feasible because, besides gamma radiation, 111In emits both therapeutic Auger and internal conversion electrons having tissue penetration ability. However, studies have shown that 111In-coupled peptides are not efficient for PRRT, as the short distance traveled by Auger electrons after emission means that decay of 111In has to occur close to the cell nucleus to be tumoricidal [65]. It was found that replacement of phenylalanine by tyrosine as the third amino acid in the octapeptide leads to an increased affinity for somatostatin-receptor subtype 2.

Peptide Vaccines

This method of treating cancerous cells relies on vaccines consisting of peptides derived from the protein sequence of candidate tumor-associated or specific antigens [66]. Tumor cells express antigens known as tumor-associated antigens

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(TAAs) that can be recognized by the host's immune system (T cells). Many TAAs have already been identified and molecularly characterized [103, 104]. These TAAs can be injected into cancer patients in an attempt to induce a systemic immune response that may result in the destruction of the cancer growing in different body tissues. This procedure is defined as active immunotherapy or vaccination as the host's immune system is either activated de novo or restimulated to mount an effective, tumor-specific immune reaction that may ultimately lead to tumor regression (Figure 9).

Several of the peptide vaccines have undergone phase I and II clinical trials and have shown promising results in immunological as well as clinical responses.

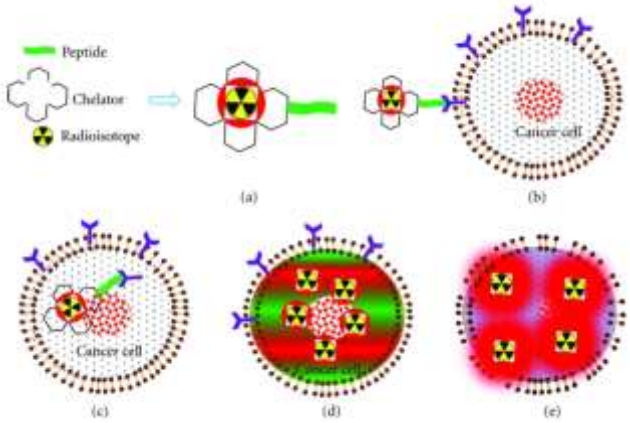

Fig. 8. Peptide receptor radionuclide therapy (PRRT); radiolabeled somatostatin analogs generally comprise three main parts: a cyclic octapeptide (e.g., Tyr3-octreotideorTyr3-octreotate), achelator (e.g., DTPA or DOTA),and a radioactive element. Radioisotopes commonly used in PRRT are 111In, 90Y, and 177Lu.

TABLE 2. Peptide receptors which have potential in cancer therapy.

Peptide receptors	Receptor subtypes	Expressing tumor type	Targeting agents
Somatostatin	sst1, sst2, sst3, sst4, and sst5	GH-producing pituitary adenoma, paraganglioma, non-functioning pituitary adenoma, pheochromocytomas	Radioisotopes, AN-201 (a potent cytotoxic radical 2-pyrrolinodoxorubicin), doxorubicin
Pituitary adenylate cyclase activating peptide (PACAP)	PAC1	Pheochromocytomas and paragangliomas	Radioisotopes, doxorubicin
Vasoactive intestinal peptide (VIP/PACAP)	VPAC1, VPAC2	Cancers of lung stomach, colon, rectum, breast, prostate, pancreatic ducts, liver, and urinary bladder	Radioisotopes, camptothecin
Cholecystokinin (CCK)	CCK1 (formerly CCK-A) and CCK2	Small cell lung cancers, medullary thyroid carcinomas, astrocytomas, and ovarian cancers	Radioisotopes, cisplatin
Bombesin/gastrin-releasing peptide (GRP)	BB1, GRP receptor subtype (BB2), the BB3 and BB4	Renal cell, breast, and prostate carcinomas	Doxorubicin, 2-pyrrolinodoxorubicin
Neurotensin	NTR1, NTR2, NTR3	Small cell lung cancer, neuroblastoma, pancreatic and colonic cancer	Radioisotopes
Substance P	NK1 receptor	Glial tumors	Radioisotopes
Neuropeptide Y	Y1–Y6	Breast carcinomas	Radioisotopes

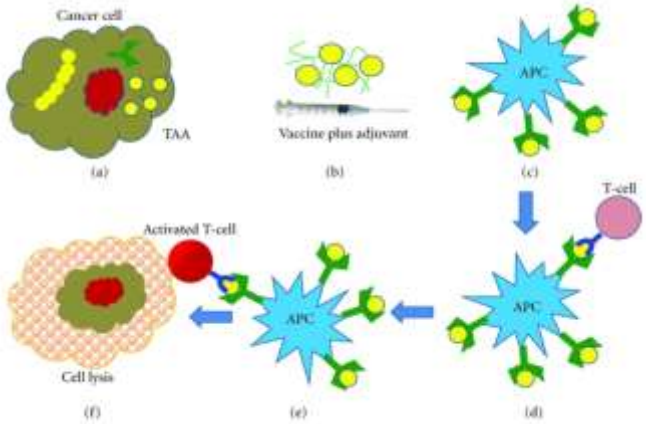

Fig. 9. Peptide-based cancer vaccines: tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the host's immune system (a). These TAAs mixed with an adjuvant can be injected into cancer patients in an attempt to induce a systemic immune response (b). The antigen 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).

Another vaccine known as GV-1001 is under development, which is an injectable formulation of a promiscuous MHC class II peptide derived from the telomerase reverse transcriptase catalytic subunit (hTERT). GV-1001 is currently undergoing phase II clinical trials for liver cancer and NSCLC (non-small-cell lung cancer) as well as a phase III trial for pancreatic cancer [126]. 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 problem of batch to-batch variation. The major disadvantage of the peptide vaccines is their weak immunogenicity. Several strategies such as 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 enhance the immunogenicity and efficacy of the peptide vaccines.

III. Pharmacological Activities of Peptidomimetics

Anti-cancer activity

Some novel unnatural amino acid-substituted (Hydroxyethyl) urea peptidomimetics which inhibited secretase, the neuronal differentiation of neuroblastoma cells and also interfered with tumorigenesis and the malignancy of neuroblastomas. Which shows that these peptidomimetics can be used as lead compounds for further development of novel anticancer drugs. [67]

Epidermal growth factor receptor (EGFR) kinase and the related human epidermal growth factor receptor-2 (HER2, ErbB2) are two growth factor receptors that have implications in cancer. The over expression or activation of HER2 occurs frequently in breast, ovarian, and lung cancers, making it an important therapeutic target in the treatment of cancer. Blocking HER2-mediated signaling with antibodies or small molecules has been shown to be effective in inhibiting cell growth. After analyzing the crystal structure of the HER2-herceptin complex, several peptidomimetics (HERP5, 6 & 7) were designed to inhibit HER2mediated signaling for cell growth. Two of the compounds (HERP5 and HERP7) exhibited antiproliferative activity, with IC50 values of 0.396 μM and 0.143 μM, respectively, against SKBR-3 cell lines (breast cancer cell lines) that overexpress HER2 protein [68].

Gastrin is a trophic factor in gastrointestinal tumors, including pancreatic cancer, which makes it an interesting target for development of therapeutic antibodies. Screening of microarrays containing bicyclic peptidomimetics by Timmerman et al. identified a high number of gastrin binders. A strong correlation was observed between gastrin binding and overall charge of the peptidomimetic. Most of the best gastrin binders proceeded from CDRs containing charged residues. In contrast, CDRs from high affinity antibodies containing mostly neutral residues failed to yield good binders. Our experiments revealed essential differences in the mode of antigen binding between CDR-derived peptidomimetics (Kd values in micromolar range) and the parental monoclonal antibodies (Kd values in nanomolar range). However, chemically derived peptidomimetics from gastrin binders were very effective in gastrin neutralization studies using cell-based assays, yielding a neutralizing activity in pancreatic tumoral cell lines comparable with that of gastrin-specific monoclonal antibodies. These data support the use of combinatorial CDR-peptide microarrays as a tool for the development of a new generation of chemically synthesized cyclic peptidomimetics with functional activity [69].

IV. Conclusion

In terms of cancer therapy, most of the available drugs develop resistance over a period of administration due to mutation. In such cases, training the body to fight cancer or injecting the tumor-associated antigen using peptide-based therapeutics that will result in an immune response to not only kill the tumor, but also provide a system response in case tumors develop in other areas, will be the ultimate therapy for cancer. In the next 10 years, peptidomimetic therapy will take a major step forward in cancer and immunotherapy. In conclusion, peptides are poised to make a huge impact in near future in the area of cancer treatment and diagnosis. Targeted chemotherapy and drug delivery techniques are emerging as an excellent tool in minimizing problems with the conventional chemotherapy. Along with different peptide-based cancer therapeutics already available for patients, a number of peptide-based therapies such as cancer vaccines, tumor targeting with cytotoxic drugs and radioisotopes, and anti-angiogenic peptides are currently on clinical trials and are expected to yield positive results. Stimuvax (palmitoylated peptide vaccine against nonsmall lung cancer), Primovax (peptide cancer vaccine, Pharmexa), Melanotan (precancerous actinic keratosis, Clinuvel), and Cilengitide (Glioblastoma, Merck) are some examples of potential peptides in late clinical trials. Due to the tremendous advancement in the large scale synthesis of peptides it will be possible to make peptide-based anti-cancer drugs more affordable to patients. In recent years combination therapy is emerging as an important strategy to fight cancer as just one method may not be efficient enough to cure the disease completely or prevent recurrence. In the hope of achieving synergistic effects, combinations of antiangiogenesis with traditional chemotherapy are currently being pursued in clinical trials. For example, cilengitide was used in a phase I/IIa combination trial, which combined cilengitide with radiotherapy and temozolomide for newly diagnosed Glioblastoma patients resulting in better overall survival (OS) rates. ATN-161 enhances the activity of radiation and chemotherapy and is progressing to a phase II trial for head and neck cancer. Encouraging data are emerging that strongly support the notion that combining immunotherapy with conventional therapies, for example, radiation and chemotherapy, may improve efficacy in cancer treatment and management.

Acknowledgement

Authors are sincerely thankful to Loknete Shri Dadapatil Pharate College of pharmacy, Mandavgan Pharata, Shirur Pune, M.S, India and Anuradha College of pharmacy, Chikhli, Dist- Buldana M.S, India for providing necessary facilities for work and authors also thankful to Lovely Friends.

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