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Review Article

PEPTIDES A NOVEL KERNEL FOR NEXT GENERATION CANCER THERAPY

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ABSTRACT
As the pervasiveness word cancer persists, the science drug development functioning barely for bring an effective therapy remains a priority in medical research. An emerging platform for the treatment of cancer with use of peptides has their possess benefits in an assortment of ways. Peptides works multiplicity mechanisms such plasma membrane disruption via micellization or induction of apoptosis via mitochondrial membrane disruption and DNA activation by Phosphorylation. This review mainly focuses on recitation the variety of peptides which are focused on cancer chemotherapy.
Keywords: Peptides, anticancer, protein, peptide vaccine

INTRODUCTION

The recent intelligence suggested that approximately 12.7 million cancers were diagnosed excluding non-invasive cancers[1]. It is believed to be about 7.9 million peoples were died in 2010[2]. This facts makes invasive cancer the leading cause of death in the world, the ever increasing the rate primarily due to an aging population and life style of modernizing world[3]. Surgery, chemotherapy, radiation therapy, and immunotherapy are the existing scenarios which are working towards the goal of complete removal of the cancer without damage to the rest of the body complementary and alternative medicine (CAM) treatments are also considered as diverse group of medical and health care systems, practices and products that are not part of conventional medicine and have not been shown to be effective[4]. The peptide therapy can be consider as the promising filed for anticancer agents they have wide benefits included designing by In silico tools are trouble-free contrast to developing a therapeutic agent by analyzing their Quantitative structure–activity relationship models (QSAR)[5]. Further the synthesis course is extremely rapid contrast to chemical compounds and peptides can be modified easily. The current research focuses on developing peptides that can serve as tumor targeting moieties and permeabilize membranes with cytotoxic consequences[6]. Interestingly the treatment option against cancer includes the used of proteins, monoclonal antibodies are encompass their own difficulty when contrast to peptides is 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 reticuloendothelial system[7]. In recent 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 60 approved peptide drugs in the market generating an annual sale of more than $13 billion[8]. 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 increasing steadily; 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[9]. There are several hundred peptide candidates in the clinic and pre clinic development. From 2000 onwards, peptides entering clinical study were most frequently for indications of cancer (18 %) and metabolic disorders (17 %)[10]. This paper is spotlighting the various modes that employing peptides in management. And special emphasis on different pharmacological mode actions which can deemed through developing of peptide.

Gastrin Releasing Peptide

Breast cancers aberrantly express gastrin releasing peptide (GRP) hormone and its cognate receptor, gastrin-releasing peptide receptor (GRP-R)[10,11]. GRP is also involved in the biology of the circadian system, playing a role in the signaling of light to the master circadian oscillator in the suprachiasmatic nuclei of the hypothalamus. Numerous of In vivo and in vitro experiments suggest that GRP, or bombesin (BBS) in mammals called neuromedin-B, the pharmacological homologue of GRP derived from amphibians, promote breast cancer growth and progression[12, 13]. Furthermore, among GRP-R expressing breast cancers with metastasis to regional lymph nodes, the metastatic deposit also maintains GRP-R expression[11]. The prevalence of these high-affinity receptors in breast cancer has led to the development of GRP-R-based diagnostic tools[14,15] as well as GRP-R-targeted therapeutics[16] and it is also plays a brilliant role in acetylcholine-mediated gastrin secretion and that nicotine-like action is not involved in gastrin secretion.

Angiocidin Inhibitory Peptides

Angiocidin, originally referred to as the CSVTCG receptor, is a tumor-associated molecule that has newly emerging as a key mediator for tumor progression[17,18]. This is functioning by the perception of "macrophage balance hypothesis," which asserts that the outcome of the interaction between macrophages and neoplastic cells depends on the number of macrophages recruited to the tumor micro environment and their state of activation. Over expression of angiocidin has been shown in many solid tumors including colorectal cancer, and increased levels of angiocidin have been demonstrated in the serum of patients with certain epithelial malignancies[19-22]. The pro-tumor effects of angiocidin are the result of myriad high-affinity binding interactions with matrix proteins, including integrins, Type 1 collagen and thrombospondin-1 (TSP-1)[23,24]. These angiocidinstromal protein binding

interactions lead to up regulation in gelatinase expression and matrix remodeling, critical elements in both angiogenesis and metastasis[25]. Further show that this pro-inflammatory activity of angiocidin is mediated through a pathway involving the activation of nuclear factor kappa B (NFκB), MAPK, and PI3-kinase. These macrophage-like cells are capable of phagocytosis and antigen presentation. These newly discovered activities of angiocidin likely contribute to its anti-tumor activity.

NK-lysin derived peptide

The peptide NK-2 is an effective antimicrobial agent with high cytotoxic activities is thus a promising candidate for clinical applications, principally the cationic core region of NK–lysin, an antibacterial protein from porcine NK- and T-cells with homologues found in human. NK-2 consists of 27 amino acid residues with an overall positive charge and adopts an amphipathic, a-helical secondary structure upon membrane interaction[26]. NK-2 is highly active against Gram-negative and Gram-positive bacteria, clinical isolates of *Candida albicans*[26], against the intracellular parasite *Trypanosoma cruzi*[27], and it can also act as effective bacterial endotoxin neutralizing agent. Alternatively, human erythrocytes, keratinocytes and glioblastoma cells have been found to be protected against cytotoxic NK-2 effects. Because of this selectivity for bacteria over normal human cells[26], the selectivity of NK-2 could be assigned to differences in the membrane phospholipid composition of the target cells[28]. Whereas the bacterial cytoplasmic membrane is characterized by a significant amount of negatively charged phospholipids, mainly phosphatidylglycerol, the human cell plasma membrane surface consists of the zwitterionic choline phospholipids PC and sphingomyelin and almost lacks anionic phospholipids[26]. Negatively charged phosphatidylserine (PS), a constituent of the inner layer of human cytoplasmic membranes, can be translocated to the surface of cells during loss of membrane asymmetry[28]. Surface exposed PS then serves as a marker for the clearance of these cells from the bloodstream by monocytes and macrophages, e.g., on athological or aged erythrocytes and apoptotic cells[29]. Though it is not well recognized, it has been shown, that also various tumor cells have elevated surface levels of negatively. Charged phospholipids[30] it is suggestive that surface-exposed PS renders these cells susceptible to killing by cationic, membranolytic peptides like NK-2.

Lunasin

Lunasin is a peptide found in soy and some cereal grains, which has been the subject of research since 1996 focusing on cancer, cholesterol and cardiovascular disease and inflammation. Epidemiological studies, animal experiments and human trials have evinced that people consuming a soy-rich diet have a lower incidence and mortality from breast cancer[31–33]. Different compounds found in soybeans have been reported to provide important protection against initiation, promotion or progression of breast cancer[34]. Lunasin is a novel 43 amino acids-peptide exhibiting the sequence, SKWQHQQDSCRKQLQGVNLTPCEKHIM EKIQGRGDDDDDDDDDD[35]. This polypeptide was originally isolated, purified, and sequenced from soybean seed in 1987, lunasin also has been found in barley, wheat and other seeds[35,36]. Lunasin's cancer preventive properties have been demonstrated in mammalian cells against chemical carcinogens and viral oncogenes[37,38]. The first animal model confirmed these preventive properties against chemical carcinogen-induced skin cancer in mice[38]. Studies focused on evaluating lunasin's mechanism of action have shown its ability to inhibit core histone acetylation and retinoblastoma protein (RB) phosphorylation[37,39]. Thus, an epigenetic mechanism has been proposed whereby lunasin selectively kills cells being transformed or newly transformed cells by disrupting the dynamics of histone acetylation–deacetylation, which is perceived by the cell as abnormal and leads to cell death[40]. Recent reports suggested that lunasin is an active cancer preventive agent using human breast cancer MDA-MB-231 cells in a xeno graft model[41]. However, lunasin's mechanism of action on well established cancer cells line has not been well defined.

Cecropins

Cecropins are significantly fine antimicrobial peptides. They were primary isolated from the hemolymph of *Hyalophora cecropia*. Cecropins lyse bacterial cell membranes, in addition they inhibit pro line uptake and cause leaky membranes. Cecropins represent a main part of the cell-free immunity of insects. Cecropins are small proteins of about 31 - 37 amino acid residues amino acids of high sequence homology active against both Gram-positive and Gram-negative bacteria[41]. These peptides have common characteristics. They are mostly constructed with α-helical structure at the amphipathic N-terminal (where one side is hydrophilic and the other hydrophobic) and the hydrophobic residues of the C-terminal. Cecropin B (CB) has the strongest antibacterial activity of this family. Previous studies have shown that CB can disrupt bacterial membranes and also kill cancer cells including leukemia, stomach carcinoma, and lung cancer cells. However, the efficacies of CB on killing cancer cells were not as good as for killing bacteria as compared with other anti-cancer agents. The possible explanation is that CB which is naturally good to kill bacteria may not be good to apply it for killing such as cancer cells.

Luteinising hormone-releasing hormone (LHRH)

The efficiency of treatment with agonists of LHRH in men with advanced stage prostate cancer was first confirmed in a clinical trial in patients with stage C and stage D prostate cancers. A fall in testosterone levels and noticeable subjective and objective enhancement was described earlier[42]. Hence early dealing with LHRH agonists causes a surge of LH release, with an equivalent augment in testosterone levels. This testosterone surge, acknowledged as the flare phenomenon, can consequence in a transient increase in prostate cancer growth, urinary obstruction, worsening of bone pain, and paralysis in patients with extensive metastasis to the spinal cord. The flare phenomenon can be prevented by short-term administration of anti-androgens[43].

Antennapedia

Many of the researchers accounted that both the retinoblastoma gene product (pRb) and p16INK4A tumor-suppressor proteins function[44] in a dissimilar cell cycle-regulatory pathways. The p16 protein may act as a cyclin-dependent kinase inhibitor by binding competitively to Cdk4 and thereby put off the interaction of Cdk4 with cyclin D1[45]. The inactivation of either the Rb and p16 gene would, therefore, abrogate an important pathway for inhibiting cell growth and thus promote tumorigenesis. Analyses of a variety of human cancers have certainly exposed a pattern of

pathway inactivation in one of the four members such as cyclin D1, Cdk4, p16 and pRb of the pRb/p16 pathway is inactivated[46,47]. Schutte *et al*.[47] have demonstrated that the pRb/p16 pathway is abrogated in 49 of the 50 pancreatic cancers (98 %) studied, all through inactivation of the p16 gene.

Ribosome-Inactivating Proteins-Ricin

Ribosome-Inactivating Proteins (RIPs) are a family of cytotoxic enzymes widely distributed in the plant kingdom. RIPs are polynucleotide adenosine glycosidases that cleave the glycosidic bond of an adenosine base in an evolutionarily conserved sequence (GAGA) located in the α-sarcin/ricin (S/R) loop of eukaryotic ribosomes. RIPs shows deprivation activity against eukaryotic and prokaryotic ribosomal RNA (rRNA) in the presence and absence of ribosomal proteins. Deprivation of the S/R loop prevents binding of the elongation factor 2 (ef 2) to the ribosome and inhibits protein synthesis. This would be a great choice to find a new peptide from RIPs for cancer targeting. Ricin, a phytotoxin protein isolated from castor seeds. The active subunit of this protein is specifically conjugated to tumor-specific antibodies which have been tested against several forms of cancer and it elicits inhibitory response on protein translation in eukaryotic cells and also causes mucosal injuries[48].

Glucagon-like peptide

Glucagon-like peptide is a nutrient-responsive neuropeptide and intestinal hormone that promotes growth, which enhances cell survival and proliferation to understand Glucagon-like peptide synthesis and expression, it must be recognized that in different cell types pro-glucagon undergoes alternative posttranslational processing, by tissue-specific processing enzymes. This clarifies how pancreatic α-cells are able to express GLP2, but predominantly produce glucagon, due to the expression of the prohormone convertase 2 (PC2)[49].

Nullomer derived peptides

Nullomers are amino acids that the human body does not exclusively code for[50], but are coding sequences which are theoretically probable[51]. These kinds of peptides can be identified by searching NCBI databases, by counted all occurrences of peptide strings, and generating a list of the smallest peptide sequences absent from natural databases. Many of New algorithms are available for negative in silico selection enables that to identify small epitopes with possible lethal effects[52].

Peptide vaccines

Certain genes (BRCA, WTetc) are expressed in an assortment of cancer types for example WT1 antibodies and WT1-specific CTLs were detected in cancer patients who are under vaccination for cancer patients, which are indicating that WT1 protein is immunogenic[54]. There are another peptide B-hCG secreted by tumors may act at quite a few diverse levels to facilitate cancer progression, as a transforming growth factor, an immunosuppressive agent, an inducer of metastasis, and/or as an angiogenic factor. Therefore, B-hCG can be used as an ideal target antigen to develop cancer vaccines for treatment of certain hormone-dependent tumors. Two imperative factors impeding the development of antitumor vaccines are the poor immunogenicity of self-tumor antigens and the low specificity of the immune responses elicited by them.

Tetraspanins

Tetraspanins, also called tetraspans or the transmembrane 4 superfamily (TM4SF), hydrophobic transmembrane domains generating two extracellular loops, intracellular N- and C-termini and two extracellular domains, one short (called the small extracellular domain or loop, SED/SEL or EC1) and one longer, typically 100 amino acid residues (the large extracellular domain/loop, LED/LEL or EC2). Although several protein families have four transmembrane domains, tetraspanins are distinct by conserved domains listed in the Protein Families database under pfam00335.12.[55] The key features are four or more cysteine residues in the EC2 domain, with two in a highly conserved 'CCG' motif. Tetraspanins are extensively concerned in cell differentiation, activation, growth, migration, and regulation of cell signaling[56,57]. This manifold purpose perhaps related with the characteristics that tetraspanins associate with various molecules including integrins, extracellular matrix proteins and other tetraspanins as an essential module of tetraspanin-mediated micro domains[58]. Recently, tetraspanins are also implicated in tumor progression and metastasis[59]. Therefore, tetraspanins have been optional as diagnostic and prognostic markers and therapeutic targets for tumor treatment.

p53

p53 is a tumor suppressor protein that in humans is encoded by the TP53 gene. This nuclear transcription factor that protects cells from replicating damaged DNA by initiating apoptosis in response to alterations in its DNA. Mutations in the DNA binding domain of p53 impair its function permitting unregulated cell proliferation accounting for half of all human malignancies[60-62]. Restoration of p53 function is an important task in cancer research. Development of nuclear transport vehicles capable of delivering therapeutics into living cells may be promising approach to restoring p53 function in cancer cells.

Fibroblast growth factor binding peptides

Fibroblast growth factors (FGFs) and their receptors control a wide range of biological functions, regulating cellular proliferation, survival, migration and differentiation. Although targeting FGF signaling as a cancer therapeutic target has lagged behind that of other receptor tyrosine kinases, there is now substantial evidence for the importance of FGF signaling in the pathogenesis of diverse tumor category. The mammalian fibroblast growth factor receptor family has 4 members, FGFR, FGFR2, FGFR3, and FGFR4. The FGFRs consist of three extracellular immunoglobulin-type domains (D1-D3), a single-span trans-membrane domain and an intracellular split tyrosine kinase domain. FGFs interact with the D2 and D3 domains, with the D3 interactions primarily responsible for ligand-binding specificity.

CONCLUSION

As the prevalence of cancer persists, the development of new and more advanced therapies remains a main concern in the health research. Novel therapies that show high specificity and enhanced potency are needed for diseases that amaze the immune system and are unresponsive to current available

treatments. The design of peptides has the potential to impact this need. Peptides, in general, are a growing class of therapeutics with over 50 products now in the market, and more in clinical trials. However the peptides are considerably less toxic than the other materials which is already exists for the issue they should considered by the researcher community for the cancer therapy.

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