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REVIEW PAPER

Peptide Therapy: A Promising Approach In Cancer Treatment

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ABSTRACT

Peptide therapy is a newly emerging promising field for cancer treatment. It draws a terrific interest now days. For cancer treatment peptide based therapy can be decided into three types mainly includes (a) Peptide-alone therapy (b) Peptide -vaccines (c) Peptide- conjugates nanomaterials. In current researches the main area of development for peptides that are able to (1) Permeate membranes with cytotoxic consequences (2) Use as tumour targeting moieties. For Apoptotic or neurotic death peptides plays an important role by forming an assembling pores which can disrupt cells or organelle membranes. Antimicrobial peptides have a very unique features of amphiphilic peptides with clusters of hydrophobic and cationic residues which have anticancer toxicity. There are so many benefits for peptide therapeutics including ease and rapid synthesis, Low molecular weight, Specificity towards tumour cells, capacity for modifications and low toxicity. But there are some challenges for development of Peptide base therapy as well like in vivo stability, low bioavailability and some restrictions in manufacturing are also present.

Key Word: Peptides therapy in cancer, necrotic death, apoptosis, cytotoxicity, drawbacks.

INTRODUCTION

Cancer is an abnormal growth of cells, it describes the disease that results when cellular changes cause the uncontrolled growth and division of cells, it also called malignancy[1-3]. More than 100types of cancer are present including breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer, and lymphoma[4,5]. There are some essential alterations in cell physiology like Insensitivity to growth- Inhibitory signals, Self-sufficiency in growth signals, Apoptosis, Sustained angiogenesis these can characterized malignancy.[6-9]

Recently a report published by World Health Organization (WHO) says that more than 10million new cancer cases are diagnosed in whole world and the rate set to be double in 2020, Cancer emerging as a major health problem in worldwide[10,11].

There are lots of current approaches present for the treatment or diagnosis of cancer like Chemotherapy, radiation therapy, surgery, biological, hormonal therapy etc. Doxorubicin, cyclophosphamide, nab – Paclitaxel are the common chemical agents used in cancer treatment ,but there are a few restrictions in cancer therapy as well like costly treatment, unavoidable side effects etc[12].

Therapeutic Peptides

Peptides are the short strings of amino acid, consisting 2 or more than amino acids, it is smaller

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than proteins. Amino acids of peptide are generally stabilized by disulfide bond. For cancer treatment peptide based chemotherapy generally divided into three types such as (a) Peptide-alone therapy (b) Peptide-vaccine (c) Peptide- conjugated nanomaterials. Peptide-alone therapy can be used to enhance the immune system response specifically for tumor cell's killing [1]. Peptide-vaccines are generally used to improve overall survival of the advanced cancer patients. Whereas peptide-conjugated nanomaterials increases the peptide's therapeutic ability by enhancing sensitivity and drug delivery in cancer treatment. Due to their ease of synthesis the peptide sequence can be modulated effortlessly [2]. There are some potential advantages of peptide therapy including easy synthesizing, small in size does can easily penetrate cell membranes, and they are also highly active, specific, affinitive, having least drug-drug interaction, biologically and chemically diverse. In numerous ways such as carrying cytotoxic drugs, hormones, vaccines, radionuclide's; peptides can be used in cancer therapy. So we can say that the peptide can be a prime option for cancer therapy and it is attracting a vast attention now a day's [1-3].

Role of peptides in cancer therapy

Now a day's peptides are the rising star amongst the anticancer agents. It can be classified into three major groups (i) Tumor targeting peptides (ii) Antimicrobial or pore forming peptides (iii) Cell permeable peptides. Tumor targeting peptides mainly target markers, expressed on the tumor cells membrane. These peptides can be successfully used in drug delivery system for its cell internalization ability. This kind of peptide therapy have a very

important role to treat lung cancer, breast cancer, melanoma, ovarian carcinoma etc [13,14]. Antimicrobial or pore forming peptides have some specific biological activities and obtained in all living organisms. These Antimicrobial peptides mainly targets cancer cell membranes and can persuade apoptotic and necrotic cell death. This pore forming peptides have potential antimicrobial activities due to its innate immune defense mechanism. Cell penetrating peptides; another type of therapeutic peptides, can be translocated through plasma membrane. These peptide plays an important role in insertion and interaction with the cell membrane and hydrophobic nature [15,16,17].

Table1: Peptides Used in cancer

SL. NO	TYPES OF CANCER	PEPTIDES
1	Pancreatic Cancer	uMMP-2anduTIMP-1 RGS6 MIC-1/GDF15 PNC-2 and PNC-7
2	Lung Cancer	LinearpeptideantigenderivedfromA NXA1 C-peptideinserum 11 novelpeptides Peptidesfromvariablepartsofantibo dies HCBP-1 BuporinIIb
3	Breast Cancer	HER-2 MUC1 NRC-3 and NRC-7 CT20p-NP Int-H1-S6A, F8A
4	Prostate Cancer	EN2 UCP2 Dox-TAT

Role of peptide therapy in pancreatic cancer

Pancreatic cancer generally occurs in the pancreatic tissue which lies in the lower part of the stomach. Pancreas releases enzymes for digestion and produces hormones for management of blood glucose level, both cancerous and non-cancerous tumor growth can occurs in the pancreas, ducts

carrying digesting enzyme can cause most common type of pancreatic cancer (Pancreatic ductal adenocarcinoma). Pancreatic cancer one of the deadliest malignant diseases in the world with 9%, 5year survival rate. According to GLOBOCAN 2018,432,242 deaths and 458,918 new cases are reported in 2018,it has been estimated that 355,317 new cases will be occurred till 2040[18,19].

For the detection of pancreatic cancer both urinary tissue inhibitor of Metalloprotease (uTIMP-1) and urinary matrix metalloprotease (uMMP-2), uTIMP-1 can also be used as a distinguisher for pancreatic neuro endocrine tumor and pancreatic ductal adenocarcinoma. Gemcitabine can be used as a first linedrug to improve the advanced pancreatic cancer patient's survival rate. Now a day's peptide based vaccines are one the prime treatment options for cancer[19-21]. Due to the ability of escaping immune system recognition of tumor cells, the clinical efficacy of peptide vaccines occurred to be limited. There are some novel modulation and potential solutions likely vaccine against multiple tumor associated antigen epitopes (TAA), TAA peptide modifications and combination of therapies[20].

By inhibiting DNA synthesis cell apoptosis induced by Gemcitabine, but current studies it has been shown that Gemcitabine with Wilm's tumor-1 peptide (WT1) is more effective than only Gemcitabine treatment. In pancreatic cancer cell WT1 is overexpressed and WT1 protein perform similarly as TAA and it has been targeted by effector T cells in immune therapies. Lastly, Gemcitabine combined with KIF20A derived peptide increases the clinical outcomes for advanced pancreatic cancer patients. In

addition Gemcitabine and Telomerase (GV1001) vaccine mixture is identified to be a safe option for pancreatic cancer patients[21-23].

Role of peptide therapy in lung cancer

Lung cancer is one of the deadliest type of cancer, with highest cancer morbidity worldwide. Lungs are situated in the chest, which take oxygen during inhalation and release carbon dioxide during exhalation. Smoking is one of the most common risk factor for lung cancer but non-smokers can have lung cancer too[24]. There are two general types of lung cancer (a) small cell lung cancer (b) non-small cell lung cancer. Small cell lung cancer is most common for heavy smokers. Whereas non-small cell lung cancer is a generalized term for various types of lung cancer including adenocarcinoma, large cell carcinoma squamous cell carcinoma[25,26]. There are some risk factors for lung cancer including family history of lung cancer, smoking, exposure to radon gas, previous radiation therapy, passive smoking. The lung cancer is 2nd most common cancer in both men and women. Mortality rate is higher than 40% in poor countries. 2.09 million new diagnosis per year and 1.76 million of deaths are reported by World Health Organization (WHO)[24-26].

Now a days new peptides have ability to detect lung cancer. Patients with diabetes, small cell lung cancer, Stage iii-iv group has highest C-peptide in their serum, as compared to control groups, in the patients with non small cell lung cancer, Annexin A1 derived peptide antigen is reported to be higher. Peptides can be used as a carriers due to specific binding site, 11Novel peptides specifically binds with human non small cell lung cancer cell line and also involved in

several numbers of pathways thus can be used as predictors for non small cell lung cancer. Peptides can be used as a biomarkers for screening of lung cancer. HCBP-1 peptide can be specifically bind to stem cells of lung cancer indicating that this peptide can be used for the identification and as a drug carriers for lung cancer. For the advance cases of non small cell of lung cancer the survival rate of the patients can be improved by using dendritic cell vaccine pulsed with Wilm's tumor-1 peptide (WT1)[27].

In recent days, peptides conjugated Nanomaterials are exhibiting a great potential for the treatment of various diseases including lung cancer. Bradykinin potentiating peptides conjugated chitosan nanoparticles can enhance the vascular permeability in tumors prolonging the survival rate and drug accumulation in tumor[26-28].

Role of peptide therapy in breast cancer

This cancer occurs in the breast cell. Breast cancer is one of the most common cancer in the women after skin cancer; though it can occurs in men also. The incident rate of these cancers increasing day by day but the mortality rate is decreasing steadily, because of early diagnosis, better screening and the improvisation in the treatment process. Breast cancer can be categorized into several types such as (a) Recurrent breast cancer (b) Inflammatory breast cancer (c) Angiosarcoma breast cancer (d) Male breast cancer (e) Ductal carcinoma insitu (f) Invasive lobular carcinoma (g) Paget's disease of the breast. (h) Lobular carcinoma insitu[29]. There are some risk factors for the breast cancer like increasing age, history of breast cancer, being female history breast condition, radiation exposure, and menstruation at

younger age, drinking alcohol, obesity, and post-menopausal hormonal therapy, unable to be pregnant. According to the World Health Organization (WHO), 11.6% of incident cases and 6.6% of mortality cases are reported until, as per WHO report 20, 697, 92 cases per year have been reported till 2018, it can be estimated that by the year of 2040 the new cases per year will reach up to 27, 788, 50[30].

For the Chemotherapy resistance cancer, immunotherapies like antibodies and peptide-vaccines can be effective treatment option. Monoclonal antibodies like Trastuzumab is one of the prime option against Human epidermal growth factor receptor 2 (HER-2), which is over expressed in most of the breast cancer patients, almost 30%. For HER-2 positive cancer patients Ado-trastuzumabis a FDA approved new therapeutic option. There are some over expressed antigens for breast cancer cells including carcino embryonic antigen (CEA), p53, HER-2, telomerase reverse transcriptase and mucin1, they can be in the detection of breast cancer as well. For the Treatment negative breast cancer (TNBC) patients personalized peptide-vaccines can be applied for the betterment of the result[30-31]. There are many strategies for the improvisation of immune efficacy including the uses of different peptide vaccine delivery system, PPV therapy, peptide sequence modifications.

There are some advantages of using vaccine delivery system including high efficiency of antigen loading, high biodegradability and biocompatibility, versatility in lipid composition and size and increased the presentation of antigen. Some investigation are reported for the development of p5

peptide encapsulation into liposome for the peptide encapsulation efficiency improvisation. For the inhibition recurrence of tumor the combination of E75 and granulocyte-macrophage colony-stimulating factor (GM-CSF) reported to be safe. For the suppression of the growth of breast cancer stem cells and prevention of tumorigenesis, ErbB-2 vaccine derived multiepitope plays an important role[32-34].

Role of therapeutic peptides in prostate cancer

Prostate cancer is a type of cancer developed in the prostate gland; it is a small walnut shape gland in the men's pelvis. It is one of the leading cause of cancer death in the men worldwide. It can be spread due to the breaking away of a prostate tumor and travelled via lymph nodes or blood vessels. There are some major risk factors for prostate cancer like ethnicity, smoking, age, family history, diet, obesity^[35]. Metastasis, erectile dysfunction, incontinence these are some of the complications with prostate cancer.

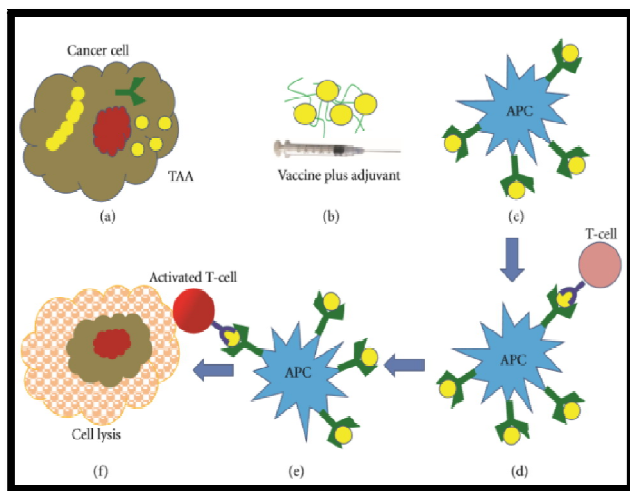


Figure 1: Peptide-based cancer vaccine treatments^[2]: Tumor cells express antigens namely tumor-associated antigens (TAAs) recognized by the host's immune system (a). TAAs mixed with an adjuvant injected into cancer patients to induce a systemic immune response (b). The antigen presenting cell (APC) introduce the antigen to T cell (c) and (d), thus the T cell is activated (e) resulting in the destruction of the cancer cell (f).

According to American Cancer Society (ACS), 174,650 new cases and 31,620 deaths have

been reported in 2019. As per data from SEER 18 it can be estimated that in 2020, 1,91,930 new cases and 33,330 deaths will be occurred. 5-year rate of survival was approximately 97.8% in between 2010-2016[36,37].

Abiraterone and docetaxel are several approaches of chemotherapy for the treatment of prostate cancer. For the chemotherapy resistant cancer immunotherapy can be a great option. The first FDA approved prostate cancer vaccine was Sipuleucel-T. EN-2, a transcription factor having homeobox, can be present in human fetus but absent in healthy adult. Overexpression of EN-2 can be used for diagnosis purpose in prostate cancer [38]. In the diagnosis of prostate cancer overexpressed mitochondrial uncoupling protein-2 can be used as a biomarker. After conducting several clinical trials it can be reported that for Castration-resistant prostate cancer (CRPC) personalized peptide vaccine (PPV) can be well tolerated, lack of knowledge for the immunological status of the patients can be a barrier for the limitation in clinical efficacy of the peptide therapy. In C57BL/6 mice the growth of prostate cancer cell can be minimized by using PAP-114-128 epitope based vaccine stimulated antigen specific T-Cell. CD4⁺ and CD8⁺ T-Cell responses can be induced by PAP-114-128 epitope peptide, screened from PAP protein, thus long peptide vaccines are more efficient. For the immunotherapy of patients of prostate tumor over expressed prostatic acid phosphate (PAP) would be an ideal option. GX-301, a multi peptide dual adjuvant telomerase vaccine is a safe option for prostate cancer now a days, consisting of Four telomerase peptide i.e. peptide540–548, peptide611–626, peptide672–686,

and peptide 766–78 and two adjuvants, Montanide ISA-51 and Imiquimod [39,40].

DISCUSSION

Now a day's cancer is a high threat to human health and for the mankind as well because of its very high recurrence and mortality rates and its metastatic characteristic. There are a variable traditional treatment for the cancer including surgical resection, radiotherapy, and chemotherapy. Amongst them chemotherapy is a helpful and frequently used option for the cancer treatment. Chemotherapy generally target tumor cell by necessary disrupting cell products like DNA, RNA or proteins but chemotherapy is itself an insufficient treatment option due to its lack of specificity to target tumor cells and for its high side effects in the patients.

Peptide based chemotherapy is gaining increase attention for the cancer treatment. Peptides can be used for the treatment of different kinds of cancers including lung cancer, pancreatic cancer, prostate cancer and breast cancer. Apart from these typical cancers; it can be used for the treatment of skin cancer, renal cancer, osteosarcoma and many more. Peptide can target tumor vessels as well as target tumor cells. In recent studies peptide based vaccines is drawing increased attention for the cancer treatment. Peptide based vaccines can be widely applied in various diseases likely allergies, infectious diseases, autoimmune diseases and cancer as well. Peptide based vaccines have so many advantages including easy administration, convenient and inexpensive therapy, specificity of targeting tumor tissues but not normal tissues and less side effects. So we can say that the peptide based vaccines or peptide therapies for cancer treatment

can improve the clinical efficacy and prolong the survival rates of the cancer patients and it will open a new path in cancer treatment.

CONCLUSION

In this review we have discussed about several types of cancers and their probable treatment options. But amongst them peptide therapies are the most relevant and have the great future prospect due to their several advantages like low toxicity, high specificity and high immunogenicity as well. So in this review we have given some insights into the peptide therapies for different types of cancers and we are hoping that the peptide therapies will definitely attract a huge attention in the cancer treatment in near future.

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