PEPTIDE BASED APPROACHES FOR CANCER TREATMENT

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INTRODUCTION

In the not too distant future, mortality from cancer will overtake that from cardiovascular disorders. There are around 7 million cancer-related fatalities each year, and by 2020, it is predicted that there will be more than 16 million new cancer cases annually and it poses a significant danger to human health as it can metastasize and has high rates of recurrence and mortality. These findings imply that cancer therapies available today are still insufficient..Tumor cells are able to evade the body's immune system and develop resistance to external treatments by producing certain proteins, among other mechanisms. Traditionally, chemotherapy, radiotherapy, and surgical resection are the methods used for treating cancer, with chemotherapy being a commonly used option. Chemotherapeutic drugs typically disrupt crucial cell components like DNA, RNA, or proteins to target tumor cells. However, chemotherapy is not entirely effective as it can cause side effects due to the lack of specificity in targeting tumor cells. Multi drug resistance (MDR) is also a major cause for chemotherapy's failure to treat patients. Given these confinements, peptide-based chemotherapy has gained attention as a potential solution.

Throughout the years, Peptides have emerged as hopeful medical options for treating various diseases such as cancer, cardiovascular diseases, and diabetes. Peptide use in other therapeutic fields is also expanding rapidly. There are presently about 60 authorized peptide drugs on the market, which generate over $13 billion in annual sales. Moreover, the number of peptide drugs that are progressing into clinical trials and are growing annually.. In the 1970s, there were 1.2 every year, followed by 4.6 every year in the 1980s, 9.7 every year in the 1990s, and 16.8 every year in the 2000s. There are hundreds of peptide candidates right now in various stages of clinical and preclinical development. Since 2000, peptides entering clinical trials have mainly focused on (17%) metabolic disorders and (18%) treating cancer .

Peptides are short chains of amino acid building blocks connected by peptide bonds. They have the ability to attach specifically to cancerous cells while generating minimal toxicity to healthy tissues. The ability of peptides to target tumors is based on their molecular structure. Tumor cells exhibit distinctive membrane proteins, such as EGFR and proteoglycans, which allow for specific binding of molecules to these proteins. Peptides, whether derived from synthetic or natural sources, can selectively attach to these proteins due to the presence of amino acids like arginine and lysine that form hydrogen bonds with the negatively charged elements on the cell membrane. However, these properties alone may not be adequate for peptides to precisely target cancer cells. The peptide's capacity to target specific cells may rely on their spatial configuration, such as the cartilage matrix proteins, which possess a three-stranded alpha-helical coiled coil structure in the C-terminal domain that might act as a trimerization site.

Peptides are considered as the most suitable molecules for binding to tumor cell membranes because of their low molecular weight and efficient uptake into cells, although other molecules can also bind to these membranes. Peptide-based chemotherapy is a form of immunotherapy, which is important because tumor cells often develop ways to evade the immune system's surveillance. The peptides utilized in cancer therapy have two main mechanisms. Firstl, peptides

have the ability to attach to particular molecular targets on tumor cells, which can either control the biosynthesis of the cells or serve as a system for drug delivery. Second, peptides can activate certain T cell reactions against cancer cells..It is worth noting that peptides have the capability to target not only malignant cells but also tumor vessels. Targeting tumor vessels with peptides may be more effective than targeting tumor cells. This is because the endothelial cells in tumor vessels have characteristics that make them more attractive targets for peptides. For example, they have lower drug resistance, a unique microenvironment, and better blood flow. These advantages also offer unique possibilities for peptide-based treatments, like direct molecular imaging of vascular peptides that have been targeted.. Additionally ,the peptide vaccine approach has several benefits, such as the cost-effective and easy procurement of peptides, ease of administration, the capacity to target only cancer cells and not healthy cells, and minimal or no adverse side effects. As a result, peptides could potentially be used for both diagnosing and treating tumors.

PEPTIDE VACCINES

Peptide-based vaccines have garnered significant attention and are one of the promising areas in which peptides help to cure cancer. The concept of cancer vaccinations has evolved over the past ten years into clinical research attempting to administer vaccines based on specific antigens in the best possible way to promote anticancer immunity. In recent times, these vaccines have been utilized for inducing regression of tumors in cancer patients.[1]

With sipuleucel-T receiving approval from the US (FDA) Food and Drug Administration as the first-ever peptide vaccine for prostate cancer, numerous clinical trials have been initiated for exploring their efficacy in other cancer types like breast cancer, melanoma, gastric cancer, and glioblastoma.

A peptide-based vaccine is a low-risk immunization method that employs artificial cancer-associated or particular peptides or peptide mixtures, all of which are intended to excite peptide-specific T cells. This approach for treating malignant cells depends on vaccinations made of peptides generated from potential tumor-associated or particular antigens' protein sequences. Tumor antigens are of two classifications : tumor-associated antigens (TAAs) or tumor-specific antigens (TSA). TAAs are often recombinant proteins or synthetic peptides, and are self-antigens which are exclusively present in tumor cells and only moderately found in normal cells. whereas, TSA comprises of antigens derived from oncoviruses as well as neoantigens that are encoded by mutations in cancer-related genes.[2]

These TAAs can be given intravenously to patients with cancer with the intention of generating a broad immune response that could potentially eliminate the cancer, which has spread to different tissues in the body. This process is known as vaccination or active immunotherapy, which involves stimulating the host's immune system to either initiate a new immune response or reactivate a pre-existing one against the tumor. The goal of this therapy is to elicit a tumor-specific immune reaction that can potentially result in the regression of the tumor. Already, a large number of TAAs have been recognised and molecularly described. The majority of TAAs are CTL epitopes, sometimes referred to as killer T cells or CD8+ T-cells.[3]

To induce antitumor immunity, peptide-based cancer vaccines need to include both CD4+ T cell epitopes that stimulate T helper cells, which help sustain the cytotoxic T lymphocytes (CTL) effector functions, and CD8+ T cell epitopes that activate CTL through the antigen cross-presentation pathway.[4] These peptides are shown on human leukocyte antigen (HLA) molecules so that CD4+ and CD8+ T cell receptors can recognise them.

Peptide vaccination utilizes two distinct kinds of peptides. One is , Short peptides, containing 8 to 12 amino acids, tend to have a short half-life and are easily degraded in serum. these peptides are able to attach to the HLA class I groove situated on the surface of cells with a nucleus,even in

the absence of specialized antigen-presenting cells (APCs). Another one is, synthetic long peptides (SLPs), typically composed of 20 or more amino acids, exhibit greater stability and immunogenicity compared to short peptides. This is because they are internalized and processed by APCs to generate peptides that can be presented by both HLA class I and II molecules, resulting in the development of potent and persistent antitumor immune responses that involve CD4+ T cells, CD8+ T cells, and B cells that produce antibodies.[5,6]

Peptide-based cancer vaccines have several advantages over traditional chemotherapy or radiation therapy.including (1) their ease of acquisition and relatively low cost; (2) simple administration; (3) their ability to target tumor tissues with specificity while sparing normal tissues; and (4) the potential for fewer or no severe side effects; (5) reduces the risk of hypersensitivity; (6) can effectively induce significant immune responses for active immunotherapy.[7]

Despite these promising results, there are still challenges to the widespread adoption of peptide-based cancer vaccines which include (1) false negative and false positive response (2) lower immunogenic potency (3) improper selection of epitopes (4) MHC restriction (5) need of adjuvant . To boost the immunogenicity and performance of peptide vaccines, a number of techniques are being investigated, including epitope augmentation, the utilization of diverse T-cell epitopes, adjuvants, ex vivo loading into antigen-presenting cells, and the integration of costimulatory molecules.

It is to be hoped that in the not-too-distant future, peptide vaccines will have larger uses due to their generally extendable advantages and compensable downsides. Phase I and II clinical trials have been conducted on several peptide vaccines, with promising outcomes in terms of clinical and immunological responses. Some notable peptide vaccines that have gone through phase I/II/III clinical trials include the Mucin-1 (MUC-1, Stimuvax) peptide (for breast or colon cancer), HER-2/neu immunodominant peptide (for breast ,ovarian, or lung cancer), Carcinoembryonic antigen (for, gastric, colorectal, breast, non-small-cell lung cancers and pancreatic),HPV-16 E7

peptide (for cervical cancer), Prostate-specific membrane antigen (for prostate cancer), Melanoma antigens (for melanoma) and Ras oncoprotein peptide (for pancreatic carcinomas and colorectal)
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A new and upcoming approach to cancer treatment involves personalized peptide-based vaccines that target neoantigens to boost the body's antitumor response. These vaccines are tailored to a person's individual cancer and are designed to elicit the immune system's recognition and destruction of tumor cells. This is achieved by delivering neoantigens to antigen-presenting cells (APCs), presenting tumor-specific neoantigens to T cells, and activating cytotoxic T cells.

Recent advancements in high-throughput sequencing (HTS) technologies offer great promise for the development of Anti-cancer peptide vaccines. These technologies are capable of detecting mutations that give rise to neo-antigens on the surface of cancer cells. These neo-antigens possess special qualities. that can boost the immune system to target cancer cells, without causing autoimmune diseases. The precise identification of these antigens, and creating vaccines based on them, holds great potential for the future of cancer treatment [8]

ANTICANCER PEPTIDE

Since the advancement of molecular biology, Several small peptides have been found in a wide variety of species. These peptides have the potential to eradicate bacteria, fungus, and tumor cells, as well as to control the immune system. With the growing accumulation of functional and structural data, a new class of low-molecular-weight peptides has emerged that exhibit anti-tumor activity. These peptides are characterized as anti-cancer peptides (ACPs). The term "anticancer peptides" (ACPs) refers to a group of short peptides consisting of 10-60 amino acids that have the ability to inhibit the proliferation or migration of tumor cells, as well as suppress the formation of

blood vessels that supply tumors. One of the benefits of using ACPs as a potential treatment for cancer is their reduced likelihood of causing drug resistance.Initially, cationic peptides were primarily studied for their antimicrobial properties, and were isolated from various organisms for this purpose. However, in 1985 it was first discovered that these peptides also possess potent anti-cancer activity, leading to a renewed interest in their potential therapeutic use.

The anti-cancer peptides are isolated from various natural sources such as medicinal plant(RA-V (deoxybouvardin),Ganoderma lucidum polysaccharide peptide (GI-PP), non-medicinal plant (Rapeseed peptide (RSP)), Streptomyces bacteria FK565 and bestatin), porcine spleen (tyroservaltide (Tyr-Ser-Val, YSV) and so on.

Anti-cancer peptides can function as either molecularly targeted peptides, which directly bind to specific cancer cells or organelles, or binding peptides that link to anticancer drugs. As molecularly targeted peptides, particularly in the α-helical form, they can penetrate the nuclear, plasma, and/or mitochondrial membranes of cancer cells, exerting pharmacological activity through various mechanisms, such as inhibiting DNA synthesis or cell division, ultimately promoting cancer cell apoptosis. On the contrary, binding peptides, also known as cancer-targeting peptides or cell-penetrating peptides, have no inherent anti-cancer properties, but can recognize and penetrate cancer cell membranes. Binding peptides can also be used for drug delivery by attaching to anticancer drugs that are otherwise impenetrable.

Due to their distinct method of action that successfully prevents tumor cell proliferation, migration, and angiogenesis, anticancer peptides (ACPs) have significant benefits over conventional chemotherapy. They can be synthesized at a low cost using solid-phase synthesis methods and are easy to modify. Additionally, ACPs penetrate the body's tissues rather deeply and seldom develop drug resistance, making them promising for clinical applications. A search of the US National Institutes of Health Clinical Trials database revealed 1002 peptide-based clinical trials targeting various kinds of cancer. A well-researched member of the bryostatin family of

peptides, bryostatin 1, has demonstrated anti-tumor effectiveness in Phase I studies for malignant melanoma, ovarian carcinoma, and lymphoma. The Phase II investigations for advanced medullary thyroid carcinoma, advanced renal cell carcinoma, small cell lung cancer and malignant melanoma have shown that Aplidine had low toxicity in the completed Phase I clinical trials. In general, ACPs are a promising replacement for conventional chemotherapy.

Although anticancer peptides (ACPs) have a number of drawbacks such as instability, limited ability to pass through cell membranes, vulnerability to being broken down by proteases, significant toxicity, and poor targeting that negatively impact their effectiveness. Their therapeutic properties can be enhanced by reconstructing or modifying them using techniques like replacing certain amino acids, fusing functional peptides together, or linking them with chemotherapeutic drugs. Due to advances in bioinformatics, proteomics, modification techniques and peptide libraries , ACPs are predicted to emerge as promising novel drugs for treating cancer in upcoming clinical applications.

PEPTIDE-DRUG CONJUGATES

Peptide-drug conjugates (PDCs) are a novel form of targeted therapy that provides enhanced tumor penetration and selectivity. They consist of three main elements: a linker, a cytotoxic payload and a homing peptide, which work together to deliver cytotoxins to the tumor cell's selected receptor. The first FDA approved PDC, ^{177}Lu-dotatate, is the only one PDC, currently available in the market for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), while many others are in various phases of development. The homing peptide, somatostatin, is linked to the cytotoxic radiotherapeutic agent ^{177}Lu via an amide linker in ^{177}Lu-dotatate.

The PDC's mode of operation is affected by factors such as the linker and homing peptide used. Several research have reported different mechanisms of action, such as You et als work on a PDC

to target metastatic breast cancer with doxorubicin, . While designing a PDC, it's crucial to keep the target and stimuli present in mind in order to create the intended mechanism of action.. Upon

entry into the tumor environment, the PDC follows a distinct path than other forms of therapy in that it is cleaved by MMP-2 prior to internalizing.

A major drawback of PDCs is their rapid renal clearance and erratic circulation stability, which is similar to peptides. To prevent systemic exposure from the early release of the cytotoxic payload, PDCs must remain stable in circulation. Several studies have investigated the utilization of various nanoparticles to enhance PDC stability. One interdisciplinary approach to enhancing stability is to attach the PDC to gold nanoparticles (AuNPs), which have advantageous physical and chemical characteristics, are safe, simple to make, and have a longer half-life in circulation. AuNPs are a useful addition to PDCs for increasing overall stability. As a whole, PDCs is a general term for a broad range of conjugates that use various peptide kinds, such as peptide-dendrimer and peptide-bicycle-toxin conjugates, both of which have demonstrated potential as drug delivery systems.

CONCLUSION

In several cancer treatments, the therapeutic consequences of drug resistance and chemotherapy are the major concerns which necessitate the development of novel therapeutic approaches. Peptides are regarded as one of the most promising therapeutic agents for tumors due to their distinctive properties, including compact size, ease of synthesis, and specificity for tumor cells. Advances in large-scale peptide synthesis and identification of novel peptides may make peptide-based anticancer drugs more cost-effective to patients. Peptide-based approaches offer several advantages, such as decreased toxicity, favorable pharmacokinetics, and efficient immunoreactivity, making them an ideal immunotherapy method for treating cancer. Peptides can be engineered for increased specificity and potency and used as drug carriers for other

therapeutic agents, directly delivering them to cancer cells.However, further study is essential to enhance peptide-based therapeutics for the treatment of cancer and overcoming challenges such as peptide stability, immunogenicity, and delivery. Despite these challenges, peptide-based approaches hold great promise as a new frontier in cancer treatment and diagnosis and are positioned to have a significant influence shortly.

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