Peptide-Based Cancer Therapeutics

Introduction

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 are growing rapidly. Currently, there are about 60 approved peptide drugs in the market generating an annual sale of more than $10 billion. Out of four peptide drugs in the market that 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 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. There are several hundred peptide candidates in the clinic and pre-clinic development. From 2000 onward, peptides entering clinical study was more frequently for indications of cancer (18%) and metabolic disorders (17%).

In conventional chemotherapy, the cancer cell-specific delivery of cytotoxic agents is difficult without affecting normal cells, which leads to systemic toxicity, causing undesirable severe side effects. “Molecularly targeted cancer therapies” using proteins, peptides, and related biomolecules are gaining momentum due to the possibility of improved drug potency and efficiency and minimal side effects. Peptides can be used as: direct anti-cancer drugs, cytotoxic drug carriers, vaccines, hormones, radio-nuclide carriers, and drug targets. Though shorter in vivo half-life of peptides is a concern, recent advances in drug delivery systems and peptide modification are expected to override those difficulties.

Emergence of Biologics in Cancer Treatment

Mortality from cancer is about to surpass that from cardiovascular diseases in the near future. About 7 million people die from cancer-related cases per year, and it is estimated there will be more than 16 million new cancer cases every year by 2020. 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). 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. So, angiogenesis inhibitors have been used to suppress tumor cell growth. 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. Drug resistance, altered biodistribution, biotransformation, and drug clearance are also common problems. Targeted chemotherapy and drug delivery techniques are emerging as a powerful method to circumvent such problems. This will allow the selective and effective localization of drugs at predefined targets (eg, overexpressed receptors in cancer) while restricting its altered biodistribution, biotransformation, and drug clearance are also common problems. Targeted chemotherapy and drug delivery techniques are emerging as a powerful method to circumvent such problems. This will allow the selective and effective localization of drugs at predefined targets (eg, overexpressed receptors in cancer) while restricting its

Table 1. LHRH agonists and new-generation antagonists available in the market.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Sequence comparison</th>
<th>LHRH (GnRHR) agonists</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abalbude</td>
<td>Ac-D(Lac)3-D-Trp-Lys-Val-Pro-Leu-Arg-Pro-Me</td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Cetrebud</td>
<td>Ac-D(Lac)3-D-Trp-Lys-Val-Pro-Leu-Arg-Pro-Me</td>
<td>Prostate cancer, breast cancer</td>
<td></td>
</tr>
<tr>
<td>Degabed</td>
<td>Ac-D(Lac)3-D-Trp-Lys-Val-Pro-Leu-Arg-Pro-Me</td>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Gannex</td>
<td>Ac-D(Lac)3-D-Trp-Lys-Val-Pro-Leu-Arg-Pro-Me</td>
<td>Prostate cancer, breast cancer, infertility treatment</td>
<td></td>
</tr>
</tbody>
</table>

Job Listings

- **Particle Sciences seeks Analytical Chemist**
- **Roche Seeking Device Development Engineer**

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anti-cancer drugs in the future, capturing the large share of the cancer therapeutic market. The "biologics" treatment options, which include the use of proteins, monoclonal antibodies, and peptides, could be free of some of the drawbacks associated with chemotherapy. Peptide therapies, in particular, are expected to be efficacious and more convenient treatment options for some types of cancer.

Recent studies have shown that peptides, due to their small size and ease of synthesis and modification, can penetrate cancer cells more easily and selectively compared to traditional chemotherapy drugs. Peptides have also demonstrated the ability to target specific cancer cells, making them a promising approach in the treatment of cancer.

Current Status & Future of Peptide Based Anti-Cancer Agents

The use of peptides as a direct therapeutic agent in targeted drug delivery and as a diagnostic tool in cancer biology is growing. Drug targeting exploits differences in the nature of normal and cancer cells and their microenvironment. This allows for the development of more specific and personalized treatment options, which can be tailored to the specific needs of individual patients.

Somatostatin Analogues in Cancer Therapy

Somatostatin analogues are the only approved cancer therapeutic peptides in the market. Some of these analogues, such as tetracosactrin (synthetic luteinising hormone-releasing hormone, LHRH), are effective in treating prostate cancer. LHRH analogues are used to inhibit the growth of prostate cancer by blocking the production of testosterone, which is required for the growth of prostate cancer cells.

Current use of peptides in cancer therapy includes the use of peptides to deliver drugs specifically to cancer cells. This is done by linking the active drug (drug-nanoparticle) to a peptide sequence that is specifically recognised by the cancer cells. This allows for the delivery of high concentrations of the drug directly to the cancer cells, while reducing the dose of the drug required to achieve therapeutic effects.

Potential of Peptides in Cancer Therapy

Peptides are a versatile class of molecules that have the potential to be used in a variety of cancer therapies. They can be used to deliver drugs specifically to cancer cells, to target cancer cells with minimal toxicity to normal cells, and to activate the immune system to fight cancer. Peptides can also be designed to deliver imaging agents to cancer cells, allowing for the detection of cancer cells in real-time.

Conclusion

The use of peptides in cancer therapy is an exciting area of research. Peptides offer the potential for highly targeted and specific treatment options for cancer, with minimal toxicity to normal cells. As research in this field continues to progress, it is likely that peptides will play an increasingly important role in the treatment of cancer.
There is a tremendous effort to discover angiogenesis inhibitors, based on polypeptides as the safest and least toxic therapy for diseases associated with abnormal angiogenesis. A number of ongoing clinical trials in this area focus on peptides derived from extracellular matrix proteins, growth factors and growth factor receptors, coagulation cascade proteins, chemokines, Type I Thrombospondin domain-containing proteins, and serpins. Recently, it was found that angiotensin-(1-7) can stop lung cancer tumor growth in mice. Also, peptides that can inhibit cell growth in drug-resistant ovarian cancer have been identified. Stapled peptides are showing promise for treating colon cancer and other forms of cancerous growth.

**Peptide Vaccines**

Active immunization seems to be the most promising strategy to treat cancer, though many approaches based on the employment of immune cells or immune molecules have been studied. Researchers have studied and debated the possibility of vaccinating against cancer for decades. Only in recent years has the debate changed from being focused on preclinical proof-of-principle to discussions on what defines a tumor antigen and how best to optimally deliver vaccines based on defined antigens to induce anti-cancer immunity. This new method of treating cancerous cells relies on vaccines consisting of peptides derived from the protein sequence of candidate tumor-associated or specific antigens. Tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the host’s immune system (T-cells). Many TAAs have recently been identified and molecularly characterized. 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 re-stimulated to mount an effective, tumor-specific immune reaction that may ultimately lead to tumor regression. Any protein/peptide produced in a tumor cell that has an abnormal structure due to mutation can act as a tumor antigen. Such abnormal proteins are produced due to mutation of the concerned gene. Clinical studies have therefore been initiated to assess the therapeutic potential of active immunization or vaccination with TAA peptides in patients with metastatic cancer. So far, only a limited number of TAAs have been clinically tested. Several melanoma TAAs have been identified and are being evaluated as peptide-based cancer vaccines in clinical trials around the world. Recent advances in the field of molecular biology have enabled the rapid identification of dozens of candidate TAAs for several important human cancers. The challenges for future studies are to determine the most efficient means of administering the vaccine and to develop methods to determine if the vaccine is effective.

**Summary**

In summary, peptides are poised to make a significant impact in the near future in the area of cancer treatment and diagnosis. A number of peptide-based therapeutics, such as cancer vaccines, tumor targeting with cytotoxic drugs and radiotopes, anti-angiogenic peptides, etc., are currently in clinical trials and expected to yield positive results. Stimuvax (palmitoylated peptide vaccine against non-small lung cancer, Merck), Primovax (peptide cancer vaccine, Pharmexa), Melanotan (pre-cancerous actinic keratosis-Clinuvel) and Cilengitide (Glioblastoma-Merck) are some examples of peptides in late clinical trials. Due to the tremendous advancement in the large-scale synthesis of peptides, it will be possible to cut down the manufacturing costs, thereby making peptide-based anti-cancer drugs more affordable.

**References**


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