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DERLEME **REVIEW**

Cancer Treatment With Peptide Therapeutics

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Abstract

Peptide therapeutics are gaining increasing attention in healthcare because of their many advantages over traditional small-molecule drugs. Peptides have advantages such as being naturally present in the body, being specific at a level that traditional drugs cannot reach, and increasing their half-life in the body. These advantages make peptide therapeutics a promising area of research for developing new treatments. According to a report on the global Peptide Therapeutics market, with a growth rate of 6.6%, the industry is expected to reach $69.3 billion by 2030. As research in this area continues to advance, peptide therapeutics will have the potential to greatly improve healthcare and patient outcomes. The versatility of therapeutic peptides enables multiple approaches to cancer treatment, and research is focused on the development of innovative peptide-based therapies. In this review, the applications of peptide therapeutics in cancer are discussed. The review also highlights the peptides used in this field, emerging opportunities in their design and development, and the future of peptide therapeutics in cancer.

Keywords: Cancer, Muc 4, Peptide therapeutics

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Peptit Terapötikleri ile Kanser Tedavisi

Özet

Peptit terapötikleri, geleneksel küçük moleküllü ilaçlara göre pek çok avantajı bulunmasından dolayı sağlık alanında giderek artan bir ilgi görmektedir. Peptitler, vücutta doğal olarak bulunmaları, geleneksel ilaçların ulaşamayacağı bir düzeyde özgüllükleri, vücuttaki yarı ömürlerinin arttırılabilmesi gibi avantajlara sahiptir. Bu avantajlar, peptit terapötiklerini yeni tedaviler geliştirmek için umut verici bir araştırma alanı haline getirmektedir. Küresel Peptit Terapötikleri pazarına ilişkin bir rapora göre, %6,6'lık büyüme oranıyla sektörün 2030 yılına kadar 69,3 milyar dolara ulaşması bekleniyor. Bu alandaki araştırmalar ilerlemeye devam ettikçe, peptit terapötikleri sağlık hizmetlerinde ve hasta sonuçlarında büyük iyileştirme potansiyeline sahip olacaktır. Terapötik peptitlerin çok yönlülüğü, kanser tedavisinde birden fazla yaklaşıma olanak tanır ve araştırmalar, yenilikçi peptit bazlı tedavilerin geliştirilmesine odaklanmaktadır. Bu derlemede, peptit terapötiklerinin kanserde uygulamaları tartışılmaktadır. İnceleme ayrıca bu alanda kullanılan peptitleri, tasarımı ve geliştirilmesinde ortaya çıkan yeni fırsatları ve kanserde peptit terapötiklerinin geleceğini ortaya koyuyor.

Anahtar Kelimeler: Kanser, Muc 4, Peptit terapötikleri

Introduction

Peptide therapeutics are a class of drugs that use peptides or polypeptides to treat diseases [2]. Peptides are naturally occurring molecules and play important roles in various physiological processes such as cell signaling and hormone regulation [3]. Peptide therapeutics are designed to modify or mimic the natural peptides for specific therapeutic outcomes. Peptide therapeutics can be synthesized with biological or chemical methods and their design can be optimized to achieve specific pharmacological characteristics [4].

Peptide therapeutics have advantages over traditional small-molecule drugs. Firstly, they are highly specific, which means they can target specific proteins or receptors with a high degree of selectivity [5]. This specificity leads to a lower risk of side effects and fewer off-target effects when compared to conventional drugs [6]. Secondly, peptides are generally well tolerated by the body with low immunogenicity and toxicity [7]. Thirdly, they can be modified to improve their pharmacokinetic characteristics (e.g., the addition of polyethylene glycol (PEGylation)) [2]. Such modifications can increase the effectiveness of the peptides in the body, decrease dosing frequency, and extend their half-life [4].

The development of peptide therapeutics involves several steps, which include target identification, design of the peptide, synthesis and modification step, preclinical testing, and clinical trials [4]. They can be designed to target many types of disease markers (e.g., cancer, autoimmune disorders, and diabetes) [8]. Preclinical testing involves evaluating the effectiveness and safety of the peptide in animal models, and clinical trials involve testing the drug in human subjects [9]. The development of peptide therapeutics can be challenging because of their potential for degradation in the body and their complex structure [10]. However, developments in modification techniques and peptide synthesis accompanied by technological developments have led to the development of many successful peptide therapeutics, which include insulin and GLP-1 receptor agonists [11].

The production of peptide drugs has increased significantly recently, with more than 60 peptide drugs approved for clinical use on a global scale [12, 13, 14, 15]. The number is predicted to continue to grow as researchers discover novel applications for therapeutic peptides and improve methods for their delivery and synthesis [2, 3]. An important area of study is the use of peptides in cancer therapy, with several peptide-based drugs that are currently in development [4]. Peptide-based drugs target specific cancer cells and show their effects by inhibiting the growth and proliferation of these cells as a promising alternative to traditional radiation therapy and chemotherapy [5] (Fig.1.). Also, these drugs offer several advantages over traditional cancer treatments. For example, increased selectivity for cancer cells, decreased toxicity to healthy cells and tissues, and improved drug delivery and pharmacokinetics. The use of peptide-based drugs is still an emerging field in cancer treatment. The results obtained in the early steps are promising, and ongoing studies strengthen the emergence of more effective and targeted treatments in the future. According to 2020 data, 19.3 million people had cancer on a global scale and this number is expected to increase to 30.2 million in 2040. Among other advantages, with their ability to participate in multiple biochemical pathways and bind to various receptors, therapeutic peptides are potential candidates. According to the FDA report, a total of 37 new peptide drug units were approved for cancer treatment in 2022, and 23 of the 37 drugs were first in their classes.

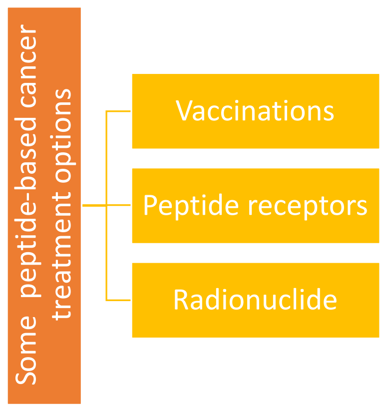

Figure 1. Some cancer treatment options using peptides

Peptide Design and Synthesis

Typically, the design and synthesis of peptides begin with the selection of the target structure and target sequence [16], which involves identifying the specific amino acid sequence to give the desired functionality or characteristics to the peptide. Peptides can be designed based on peptide sequences that are derived from natural proteins or depending on the desired implementation. The amino acid composition and length of a sequence will influence whether stability and correct folding can be achieved [17]. Molecular dynamics simulations or computational modeling can be employed to predict the stability and structure of the target peptide.

After the target sequence is determined, the next step is to select the appropriate synthesis method [18]. Various methods exist for peptide synthesis (e.g., Natural Chemical Ligation (NCL), Solid-Step Peptide Synthesis (SPPS), and Liquid-Step Peptide Synthesis (LPPS)). The most widely used method is SPPS because of its efficient, simple, and versatile features [19]. The choice of synthesis method depends on several factors (e.g., complexity and length of the target peptide, desired purity, equipment, yield, and availability of reagents).

The peptide must be characterized and purified following the synthesis to ensure its consistency and quality [], which involves using Mass Spectrometry (MS), High-Performance Liquid Chromatography (HPLC), and Nuclear Magnetic Resonance (NMR) spectroscopy techniques to confirm its purity, identity, and structure [21,22]. The purification process can be difficult because of the presence of by-products and impurities and may involve a multitude of chromatography and other separation techniques [16]. After it is purified and characterized, the peptide can be used for a wide variety of purposes such as diagnostics, drug discovery, and biotechnology [23].

Applications of Peptide Therapeutics in Cancer

Peptide drugs consist of short chains of amino acids and can effectively inhibit the growth and proliferation of cancer cells by targeting their specific receptors or proteins [24]. Peptide drugs have shown potential in the treatment of various cancers (e.g., lung cancer, breast cancer, and pancreatic cancer) [24, 25]. Although more studies are needed to understand the potential of peptide drugs in cancer treatment fully, these discoveries are promising for the development of novel and effective treatments.

These drugs work by targeting specific cancer pathways or cells and provide a more effective and targeted approach to cancer treatment compared to chemotherapy. Peptide therapeutics can also decrease side effects that are commonly associated with cancer treatment and minimize toxicity to healthy cells [26]. This targeted approach offers patients personalized and effective treatments with the potential to revolutionize cancer treatment.

Cancer is a global healthcare concern with many new cases diagnosed every year [27]. The use of peptide therapeutics is increasing in cancer treatment, and the peptide drug market is predicted to grow significantly in the future [27]. Despite the effects of COVID-19 on the growth of the peptide therapeutics market, the therapeutic effect of peptide drugs has allowed this demand to continue [28].

Peptides show their anti-cancer effects over various mechanisms of action. One of the most common mechanisms is programmed cell death or apoptosis triggered by peptides in cancer cells [29]. Peptides also target specific signaling pathways involved in cell survival or growth, inhibiting cancer cell proliferation [30]. Also, peptides can stimulate the immune system to recognize and attack cancer cells and result in increased tumor cell killing and positive outcomes [31]. These mechanisms of action have made peptide therapy a promising means of cancer treatment, with the potential for use in combination with other cancer treatments to improve patient outcomes [32, 33].

Peptide receptors

Peptide receptors are a type of membrane-bound receptors activated by extracellular proteins or peptide ligands [34] as a large group of G Protein-Coupled Receptors (GPCRs) involved in diverse physiological processes and are expressed in various tissues throughout the body. These receptors are characterized by their ability to bind and respond to specific peptide ligands, initiating a signaling cascade across the cell membrane [35]. In particular, the Neuropeptide Y-Receptor plays roles in the initiation and maintenance of feeding behavior eliciting hunger or satiety [36].

Peptide receptors activate various signaling pathways upon ligand binding (e.g., the Cyclic Adenosine Monophosphate (cAMP) pathway, Mitogen-Activated Protein Kinase (MAPK) pathway, and Inositol Triphosphate (IP3) pathway) [35]. These signaling pathways also enable the activation of the downstream effectors resulting in changes in cellular function and behavior. The specific signaling pathway activated by a peptide receptor depends on the subtype of the receptor and the specific ligand [37]. For example, the formyl peptide receptor family is associated with complement peptide receptors, and these receptors are more distantly associated with chemokine receptors [38].

Peptide receptors play important roles in various physiological processes (e.g., metabolism, immune function, and cardiovascular regulation) [39]. The dysregulation of peptide receptors has been associated with cancer, diabetes, and many other diseases (Figure 2) [40]. For example, RXFP2 peptide receptor activation increases the intracellular cAMP, initiating signaling over β-catenin, which is involved in various processes [41]. Understanding peptide receptors has led to the development of several drugs that target these peptide receptors [38]. In brief, peptide receptors are important components of cellular signaling pathways, playing vital roles in maintaining physiological homeostasis and holding promise for drug intervention in various diseases.

Peptide receptors	Receptor subtypes	Expressing tumor type	Targeting agents
Neurotensin	NTR1, NTR2, NTR3	Small-cell lung cancer, Neuroblastoma, Pancreatic and Colon Cancer	Radioisotopes
Pituitary Adenylate Cyclase Activating Peptide (PACAP)	PAC1	Prostate, Pancreatic Ducts, Liver and Bladder Cancers	Radioisotopes, Doxorubicin
Vasoactive Intestinal Peptide (VIP/PACAP)	VPAC1, VPAC2	Lung, Stomach, Colon, Rectum, Breast, Prostate, Pancreatic Ducts, Liver and Bladder Cancers	Radioisotopes, Camptothecin
Bombesin/Gastrin-Releasing Peptide (GRP)	BB1, GRP Receptor Subtype (BB2), BB3 and BB4	Renal Cell, Breast, and Prostate Carcinomas	Doxorubicin, 2-pyrrolinodoxorubicin

Figure 2: Some cancer peptide receptors used

Cancer-protective peptides and their potential benefits

Cancer-protective peptides have been identified with potential benefits in the prevention and treatment of cancer [42]. These peptides occur naturally in various sources (e.g., animals, plants, and microorganisms) [43] and are considered to exert their effects by inhibiting tumor growth, increasing the ability of the immune system to fight cancer cells, and promoting cell death [44]. These peptides have recently attracted attention because of their potential to provide a non-toxic alternative to traditional cancer treatment modalities. The sources of peptides are diverse and include both animal and plant-based ingredients [45]. For example, some vegetables such as soybeans, and some animal products such as milk and eggs contain cancer-protective peptides [42, 46]. Microorganisms such as fungi and bacteria were also found to produce cancer-protective peptides [47]. The broad spectrum of these peptide sources provides an opportunity for the development of cancer treatment and preventive measures.

In the treatment and prevention of cancer, the potential benefits of cancer-protective peptides are extensive [48]. Studies show that these peptides can induce apoptosis (programmed cell death) in cancer cells, inhibit tumor growth, improve the immune system's ability to fight cancer cells, increase the effectiveness of chemotherapy and decrease side effects, decrease inflammation, [43] Considering the benefits of these peptides, the potential for cancer treatment is an exciting possibility [49].

The role of Artificial Intelligence in peptide research

With its high efficiency and accuracy, Artificial Intelligence (AI) demonstrated great potential in the field of peptide studies by enabling the identification of peptide sequences [50]. The identification of peptides that have specific characteristics has been an important step in the development of peptide-based therapeutics. In this context, peptides also showed great potential in the treatment of many diseases, including cancer, autoimmune disorders, and diabetes [51]. Artificial Intelligence algorithms analyze large datasets and can identify patterns that are not easily understood by humans, and result in the identification of novel peptide sequences harboring desired characteristics. For example, Machine Learning Methods were used to predict the activity of antimicrobial peptides that can be used to develop new antibiotics [52].

AI can also be applied to predict peptide functions and structures. Understanding the function of a peptide and predicting its structure is important for new peptide designs with specific characteristics [53]. Artificial Intelligence algorithms predict peptide structures with high speed and accuracy and allow researchers to discover peptides that have desired characteristics quickly. For example, Deep Learning was used to predict peptide-protein interactions, which can be employed to develop peptide-based therapeutics [54]. AI can also be used to optimize the therapeutic safety and efficacy of peptides by predicting their pharmacodynamic and pharmacokinetic characteristics [53].

AI can also be used to design novel peptides that have the desired characteristics. AI Algorithms analyze large datasets of peptide sequences and identify relationships between amino acid sequences and peptide characteristics and in this way, novel specific peptides can be designed with increased bioactivity or stability or improved pharmacokinetics [54]. AI can also be employed to optimize peptide sequences for use and improve their therapeutic safety [54] and to predict the potential toxicity of novel peptides, reducing the risk of adverse effects in clinical trials [55]. In general, AI will accelerate the development of peptide-based therapeutics.

Artificial Intelligence (AI) has the potential to transform the field of drug discovery, including the optimization and design of peptide-based drugs. AI algorithms can learn patterns from large amounts of data, and allow researchers to identify promising peptides for drug development more quickly [56]. Rapid Novor, the first AI-enabled drug discovery company that has a commercially validated platform, has already demonstrated the power of AI in peptide discovery [57]. Researchers can accelerate the drug discovery process by leveraging AI and enabling the development of more targeted peptide-based therapeutics.

Peptide-based therapeutics have a promising future for the treatment of several diseases such as cardiovascular diseases, cancer, immune disorders, and gastrointestinal dysfunctions [58]. Artificial Intelligence can help develop therapeutics by identifying novel peptides with specific characteristics such as high selectivity and potency. Researchers can also develop more effective treatments for various diseases by engineering these peptides. The same could be achieved for a wide range of drugs (e.g., Peptilogics) by using AI to explore unused chemical space and treat some of the most challenging diseases [59]. The potential of peptide therapeutics is huge, and Artificial Intelligence will help uncover new possibilities in this field.

Artificial Intelligence can be used in drug discovery and peptide-based therapeutics, as well as biomedical imaging and diagnostics. The algorithms of Artificial Intelligence can help detect diseases such as cancer and Alzheimer's by analyzing medical images. In this way, more accurate diagnostic tools can be developed and diseases can be detected at earlier steps. Artificial Intelligence can also help develop personalized medicine, in which treatments are tailored to genetic structure and disease characteristics [60].

In conclusion, peptide therapeutics are a promising treatment option for cancer as an advantageous factor because of their low toxicity, ability to target specific cancer cells, and their high specificity. The development of peptide therapeutics has led to the synthesis and design of various cancer peptide therapeutics (including Nivolumab, Ipilimumab, and Pembrolizumab). Previous applications of peptide therapeutics in cancer showed promising outcomes with the global use of cancer therapeutic drugs. The future of peptide therapeutics seems bright. Studies underway and developments in the field will lead to the discovery of improved and novel peptide therapeutics for cancer treatment, and peptide therapeutics and cancer treatment options will continue to be one of the areas attracting attention.

Author contribution:

Emel Savul: Contributed to the preparation of the draft of the article, literature review, and presentation of the final version of the article.

Prof. Dr. Berrin ERDAĞ; He contributed to the creation of the idea of the article, review of its scientific content, preparation of the article for publication, and approval of the final version.

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