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Innovative applications of oligopeptides in drug delivery systems: Strategies, progress and challenges

Aozhong Jiang

School of International Education, Beijing University of Chemical Technology, Beijing, China

2022090022@buct.edu.cn

Abstract. Targeted drug delivery systems play an important role in new drug development. Oligopeptides, as an excellent drug delivery medium, have great biocompatibility, targeting ability, and functionalized modifications. Therefore, oligopeptides have shown great potential for application in diverse pathological conditions such as cancer, inflammatory diseases, and cardiovascular diseases, and have begun to be used in clinical therapy. This review provides a comprehensive overview of the development and applications of oligopeptide drug delivery systems and analyzes the excellent properties of oligopeptides as well as the challenges. Further research is needed to optimize the biocompatibility of oligopeptides, improve their targeting and solubility, as well as explore other new application areas.

Keywords: Targeted drug delivery systems, Oligopeptides, Biocompatibility, Pathological conditions, Optimization

1. Introduction

Drug delivery systems (DDS) play an essential role in drug development, enabling precise action on target tissues or cells, reducing impacts on non-target tissues, and enhancing treatment accuracy. Traditional DDS, such as oral and injectable ones [1], fail to meet societal needs due to poor targeting, slow onset, and high side effects. The urgent need for effective targeted DDS prompted exploring oligopeptides as drug carriers [2], exhibiting superior biocompatibility, targeting abilities, and functionalization modification [3]. Oligopeptide-based DDS, proven effective in treating various diseases like cancer [4], inflammatory, autoimmune diseases and Alzheimer's diseases [5,6], are central to new DDS R&D efforts. This review aims to summarize the strategies and applications of oligopeptide DDS, analyze the challenges in their development, and project their future. We hope this review underlines the significance of oligopeptides in DDS and propels their clinical applications.

2. Strategies for the use of oligopeptides in drug delivery

Oligopeptides' exceptional properties enable researchers to tailor them for precise spatiotemporal targeting and more efficient, safe therapeutic effects, emphasizing the importance of developing novel strategies for oligopeptide drug delivery. Leveraging these properties, researchers have embarked on various exploratory applications of oligopeptides for precise targeting, improved cellular penetration, and self-assembled oligopeptide-based nanocarriers, thereby advancing innovative strategies for oligopeptide drug delivery and examining their clinical application potential (Figure 1).

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2.1. Targeted delivery

Some oligopeptides can specifically bind to certain cell surface receptors or other molecules in order to selectively deliver drug molecules to the designated site, a process known as "targeted delivery [7]. Zhao et al. [8] have shown that a tripeptide consisting of Arg-Gly-Asp (RGD) can bind to integrin receptors to inhibit the expression of ECM glycoproteins (e.g., fibronectins and fibrinogen) and reduce tumor formation. In addition, according to Valentinis [9], Xu [10] , and Kessler [11] et al, another targeting peptide, Asn-Gly-Arg (NGR), specifically binds to CD13 in the tumor vasculature, leading to caspases-mediated apoptosis or thrombus formation in the tumor vascular system, which ultimately leads to tumor cell death and tumor infarction.

2.2. Cell penetration

The limited ability of drugs to penetrate into target cells is a major obstacle to drug delivery [7]. Without sufficient intracellular accumulation of targeted cells, drugs often fail to achieve the desired therapeutic outcomes. The discovery of cell-penetrating peptides (CPPs) solves this problem well: they can be taken up by cells through endocytosis and direct translocation without destroying the integrity of the cell membrane [12]. A notable example of this strategy is demonstrated by Kwon and colleagues [13], who designed a TAT-asparaginase complex that is effective against lymphoblastic leukemia, and their experiments demonstrated that the TAT-asparaginase complex was able to penetrate a hepatocyte cell line (HeLa) and a MOLT-4 tumor cell line with significant efficiency, while the TAT structural domain also showed considerable drug delivery capacity to transport various drugs across the membranes of multiple cell types. Additionally, He et al. [14] showed that a drug delivery system coupled to the cell-penetrating peptide octa-arginine (R8) could deliver small interfering RNAs to treat cancer, and about 80% tumor volume inhibition was observed in experiments with HepG2 tumor-bearing mice.

2.3. Design of self-assembled oligopeptide-based nanocarriers.

Macromolecular self-assemblies made of oligopeptides are considered promising drug delivery vehicles for numerous applications due to their ease of synthesis and functionalization as well as their inherent biocompatibility [15]. For instance, hydrophobic drugs with poor water solubility have low bioavailability, thus limiting possible applications and formulation development [16]. The success of such drugs as bioavailable therapeutic agents largely depends on the development of a drug delivery system that improves their water solubility, and self-assembled oligopeptide-based nanocarriers largely solve this problem. Li et al. [16] showed that their synthesized star block copolymers in the form of hydrophobic oligopeptide (HOP)-based PEI-g-(HOP-b-PEG) can self-micellize in aqueous solution and have some loading capacity for hydrophobic drug molecules (e.g., DOX, etc.), which has the potential to be used as poorly water-soluble drug nanocarriers. In addition, Shadab and colleagues [17] attempted to load curcumin into their self-synthesized novel self-assembled dipeptide NPs derived from methionine-dehydrophenylalanine, and they showed that the dipeptide could improve the water solubility and bioavailability of curcumin and enhance its toxicity to cancer cells. Featuring high drug-loading efficiency and sustained release capability, these nanoparticles provide an extended therapeutic window, such innovative designs highlight an effective delivery system that can be used for cancer therapy.

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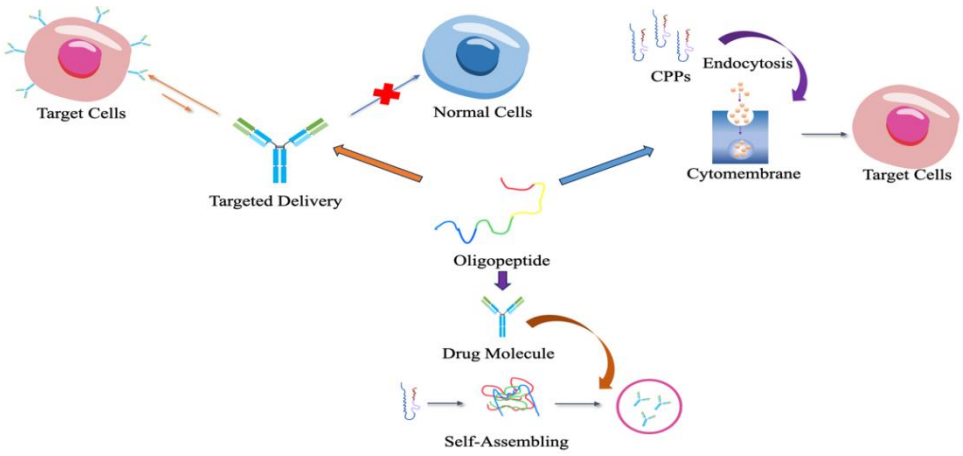

Figure 1. Strategies for the application of oligopeptides in drug delivery, including targeted delivery, as cell-penetrating peptides (CPPs), stimuli-responsive and self-assembling peptides.

3. Oligopeptide delivery systems in the treatment of diseases

Ongoing research on oligopeptide drug delivery systems has broadened their disease treatment applications. These systems have been extensively applied in treating diseases like cancer, inflammatory and autoimmune disorders. Notably, Takeo et al. [18] used a humanized HeLa-hPepT1 mouse model to study oligopeptide drug tumor targeting. Their research involved intravenously injecting anti-hydrolyzed peptide ^{3}H and peptide-mimetic anticancer drug, bestatin, showcasing significant cancer inhibition both *in vivo* and *in vitro* (Figure 2). This provides evidence for oligopeptide transporter activity use in tumor cell targeting and sets a precedent for oligopeptide-based tumor-targeted therapy. Léonard et al. [19] found that a cell-penetrating peptide, RT53, selectively kills cancer cells while sparing normal cells. Also, Yasufumi et al. [20] developed a doxorubicin-bound liposome modified with WIFPWIQL peptide that accumulated in tumor endothelial cells *in vivo*, significantly inhibiting tumor growth, and further illustrating oligopeptides' potential in cancer treatment.

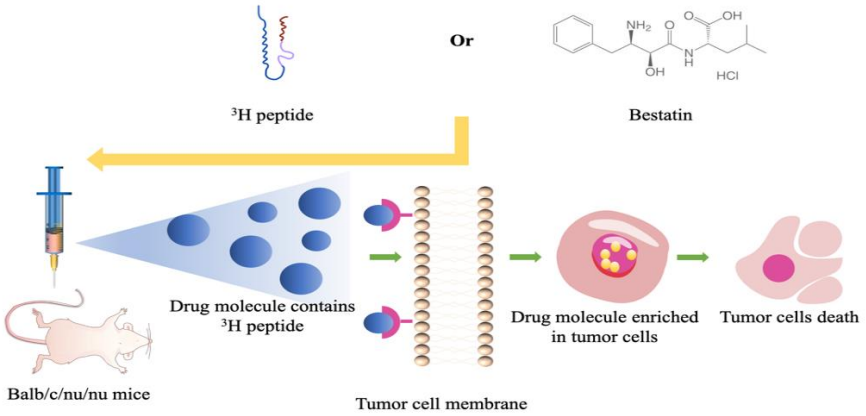

Figure 2. Precise targeting of oligopeptides to tumor cells and cancer inhibition by the peptide mimetic drug Bestatin.

Inflammatory and autoimmune responses serve as the body's protective reaction, yet their prolongation can trigger serious pathological conditions. This process involves a complex cytokine network, including interleukins (IL) [21] and interferon (IFN), which maneuver intracellular signaling pathways, initiating an *in vivo* inflammatory response. A study by Delgado et al. [5] discovered that vasoactive intestinal peptide (VIP), effective against inflammation and autoimmune diseases, inhibits inflammatory responses via the cAMP/PKA-dependent and independent pathways by binding to the

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VPAC1 receptor. Moreover, VIP inhibits inflammatory factors' gene expression, such as TNFα, and restrains inflammatory gene expression by diminishing NF-κB's transcriptional activity. Furthermore, VIP increases the expression of genes inhibiting the inflammatory response. VIP has also been found effective in preventing various inflammatory pathological conditions like rheumatoid arthritis (RA) [22], under which cytokines like TNFα and IL-6 are overproduced. With its ability to reduce these cytokines in animal models, VIP presents a promising biotherapeutic approach for treating inflammatory and autoimmune diseases (Figure 3).

Delving into oligopeptides' utility in inflammation therapy, Zhang et al. [23] unearthed that a small 41 amino-acid peptide, DAvp-1, extracted from the sharp nose pit viper's venom via the phage display method, effectively binds to TNF-α's receptor, TNFR1, thereby inhibiting inflammation [24]. Similarly, Guo et al. [25,26] identified Hydrostatin-SN1, a short 22 amino-acid peptide, that binds to TNFR1 both in vitro and in vivo, yielding anti-inflammatory effects by inhibiting MAPK and NF-κB pathways [27,28]. These findings underscore the applications of oligopeptides in treating inflammatory conditions, illuminating their potential for use in inflammation therapy (Figure 3).

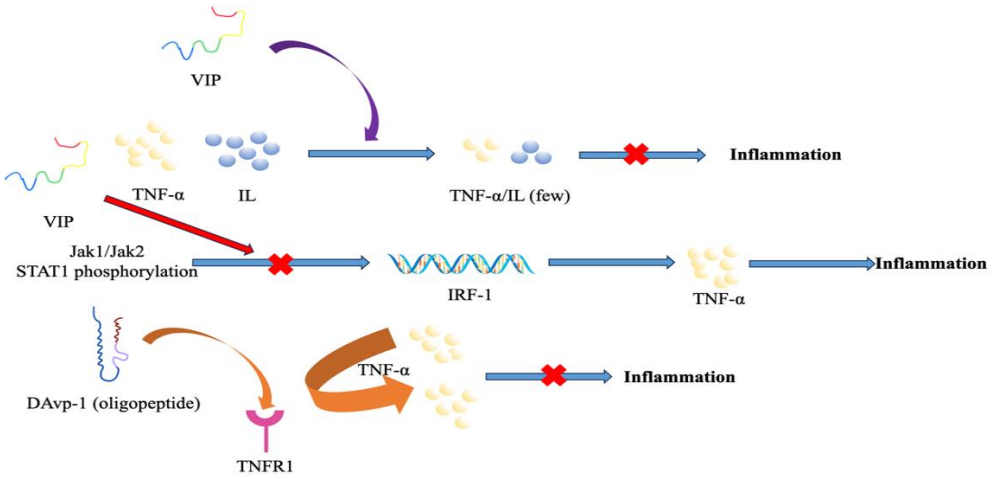

Figure 3. Oligopeptide drugs VIP and DAvp-1 have an inhibitory effect on the inflammatory response.

In neurodegenerative conditions like Alzheimer's disease (AD), oligopeptide-based drug delivery systems have demonstrated effectiveness. Gandy's study [29] identified p3-Alcβ, a small peptide deriving from γ-secretase cleavage of Alc protein, crucial for neuroprotection. By inhibiting NMDA receptor signaling, mitigating Ca^{2+} entry, neutralizing Aβ oligomer toxicity, and restoring mitochondrial balance, it counteracts Aβ-induced neurodegeneration. These neuroprotective functions of p3-Alcβ have been validated in both mouse and primate models. Furthermore, Manea et al. [30] discovered that sequential oligopeptides and lysine dendrimers conjugated with β-amyloid (4-10) epitope peptide could serve as a new vaccine lead structure against AD. These findings highlight the potential of oligopeptides in AD therapy.

4. Challenges and future prospects

Oligopeptide drug delivery systems (ODDS) present rewarding therapeutic potential but also pose challenges. Biocompatibility, a key issue, enables safe and efficient therapy and peripheral damage minimization to healthy tissues. However, studies have revealed instances where these systems can stabilize peptide components, impacting cell permeability, and possibly safety and efficacy. Setting up a safety assessment mechanism for ODDS and evaluating in vivo metabolic behavior and safety through comprehensive animal experiments are crucial.

Drug loading and release efficiency of ODDS also limit their development. Studies suggest that self-assembled peptide-drug couplings (SPDCs) have better developmental prospects for their superior drug-

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loading, excellent biodegradability, and successful in vitro performance. Yet, improving the loading capacity and release efficiency of ODDS remains a research focus.

For widespread utilization of ODDS, cost-effective large-scale production is essential. Jafari et al. [31] demonstrated that the mass-production feasibility of cell-penetrating peptide dendrimers (DCCPs) based on branched CPPs, but scaling up other ODDS needs exploration.

In conclusion, oligopeptides, essential life components, serve indispensable physiological roles and act as excellent drug carriers in pathological states. Despite challenges, ODDS demands further research due to their excellent biological activity, structural diversity, and targeting or therapeutic roles. Despite obstacles hindering their mass application, their potential highlights their need for increased attention and research.

5. Conclusion

Oligopeptides, short-chain amino acid sequences, demonstrate good biocompatibility, biodegradability, structural diversity, and targeting ability, making them potent for drug delivery. After being subjected to chemical modifications and nanoparticle preparations, they have been used in treating tumors, and neurodegenerative, inflammatory, and autoimmune diseases, with potential usage in smart polymer switches and antimicrobial therapeutics. However, before clinical application, challenges like low biostability and bioavailability due to enzymatic degradation, possible immune responses causing immunotoxicity or quick drug clearance, complex and expensive production processes, and inadequacy of in vivo transport behavior studies need to be addressed. Future research should focus on improving stability, reducing immune reactions, easing production, and conducting thorough animal experiments to assess metabolic behavior and safety.

References

[1] Sultana, Zare, Thomas, Kumar and Ramakrishna 2022 *Medicine in Drug Discovery* 15 100134.
[2] Hudecz, Banoczi and Csik 2005 *Med Res Rev* 25 679-736.
[3] Todaro, Ottalagana, Luin and Santi 2023 *Pharmaceutics* 15 1648.
[4] Rizvi, Zhang, Zhang and Fang 2024 *ACS Pharmacol Transl Sci* 7 309-334.
[5] Delgado, Abad, Martinez, Juarranz, Arranz, Gomariz and Leceta 2002 *J Mol Med (Berl)* 80 16-24.
[6] Delrieu, Ousset, Voisin and Vellas 2014 *Rev Neurol (Paris)* 170 739-748.
[7] Berillo, Yeskendir, Zharkinbekov, Raziyeva and Saparov 2021 *Medicina (Kaunas)* 57 1209.
[8] Zhao, Santino, Giacomini and Gentilucci 2020 *Biomedicines* 8 307.
[9] Valentinis et al. 2019 *Int J Mol Sci* 20 4511.
[10] Xu et al. 2019 *Int J Oncol* 55 823-832.
[11] Kessler et al. 2018 *Transl Oncol* 11 1271-1282.
[12] Tesauro, Accardo, Diaferia, Milano, Guillon, Ronga and Rossi 2019 *Molecules* 24 351.
[13] Kwon, Li, Liang, Park, Chang and Yang 2008 *J Control Release* 130 252-258.
[14] He, Guo, Wu, Chen, Wang, Liu and Ju 2019 *Biomaterials* 225 119501.
[15] Ji et al. 2017 *J Drug Target* 25 597-607.
[16] Li, Li, Xu, Zhang and Liu 2013 *Colloids Surf B Biointerfaces* 110 183-190.
[17] Alam, Panda and Chauhan 2012 *Int J Nanomedicine* 7 4207-4222.
[18] Nakanishi, Tamai, Takaki and Tsuji 2000 *Int J Cancer* 88 274-280.
[19] Jagot-Lacoussiere, Kotula, Villoutreix, Bruzzoni-Giovanelli and Poyet 2016 *Cancer Res* 76 5479-5490.
[20] Katanasaka, Ishii, Asai, Naitou, Maeda, Koizumi, Miyagawa, Ohashi and Oku 2010 *International Journal of Cancer* 127 2685-2698.
[21] Boesen 2013 *American Journal of Physiology-Renal Physiology* 305 F189-F198.
[22] Delgado, Martinez, Pozo, Calvo, Leceta, Ganea and Gomariz 1999 *The Journal of Immunology* 162 1200-1205.
[23] Zhang, Liu and Tang 2022 *Toxins (Basel)* 14 155.

DOI: 10.54254/2753-8818/49/20241283

[24] Kaminska 2005 *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* 1754 253-262.
[25] Zhang et al. 2020 *Front Pharmacol* 11 930.
[26] Zhang, Tang, Chen and Liu 2022 *Int J Mol Sci* 23 8554.
[27] Zheng et al. 2016 *Mediators Inflamm* 2016 9348037.
[28] Wu et al. 2017 *Front Pharmacol* 8 246.
[29] Gandy 2023 *Trends Mol Med* 29 487-488.
[30] Manea, Przybylski, Hudecz and Mezo 2008 *Biopolymers* 90 94-104.
[31] Jafari, Maleki Dizaj and Adibkia 2015 *Bioimpacts* 5 103-111.