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The Research Progress and Challenges of Peptide Drugs in the Treatment of Non-Small Cell Lung Cancer: From Mechanism to Clinical Practice

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ABSTRACT

Non-small cell lung cancer (NSCLC) is the most common lung cancer subtype, with rising incidence and poor prognosis due to difficult early diagnosis. Peptide drugs, known for their high selectivity, low toxicity, and flexible structure, are emerging as promising NSCLC treatments. This review covers recent advances in peptide drugs, focusing on mechanisms for targeting pathways, modulating immunity, and overcoming resistance. Challenges such as stability, bioavailability, and delivery efficiency are discussed, alongside strategies like chemical modifications, nanocarriers, and computational design to improve efficacy. Future prospects include combining peptide drugs with current therapies and utilizing AI for precise NSCLC treatment.

KEYWORDS

Non-small cell lung cancer (NSCLC); Peptide drugs; Targeted therapy; Immune modulation

1. INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer, accounting for approximately 85% of all lung cancer cases (Siegel et al., 2020). In recent years, the global incidence of NSCLC has been steadily increasing, particularly in developing countries. The accelerating pace of industrialization and rising smoking rates have contributed to the growing number of NSCLC cases. In the United States, the incidence is slightly higher in men than in women, though the number of female cases is also rising, largely due to increased smoking rates among women (Jemal et al., 2004). Additionally, NSCLC is more frequently diagnosed in middle-aged and older adults over 55, while younger patients (under 40) are relatively rare but often exhibit different clinical characteristics (Subramanian & Govindan, 2010).

Globally, numerous organizations and research institutions, such as the International Association for the Study of Lung Cancer (IASLC) and the Global Lung Cancer Coalition (GLCC), are committed to advancing research and treatment for NSCLC, driving rapid developments in precision medicine and personalized therapy (Herbst et al., 2018). Nonetheless, NSCLC's early symptoms are usually subtle, including persistent cough, chest pain, shortness of breath, and weight loss, often only becoming noticeable at an advanced stage. This makes early diagnosis challenging, and many patients are diagnosed at a late stage with a poor prognosis (Goldstraw et al., 2016).

Peptide drugs have emerged as a novel therapeutic approach, garnering significant attention for their unique biological properties. Compared to small molecule and antibody drugs, peptide drugs offer advantages such as high selectivity, low toxicity, and ease of design and modification, showing immense potential in targeting cancer cell signaling pathways, modulating immune responses, and overcoming drug resistance (Fosgerau & Hoffmann, 2015). However, challenges such as stability,

bioavailability, and delivery efficiency remain. This review systematically examines recent research advances in peptide drugs for NSCLC treatment, focusing on their mechanisms of action, and discusses challenges in clinical application and future research directions to provide a theoretical basis for further development (Otvos & Wade, 2014).

2. NSCLC AND GENE MUTATIONS

The development and progression of NSCLC are closely linked to various driver gene mutations, which lead to uncontrolled cell proliferation and eventually tumor formation. Mutations in the epidermal growth factor receptor (EGFR) gene are among the most common genetic alterations, especially prevalent in Asian patients, accounting for about 50% of all cases (Zhang et al., 2019). These EGFR mutations primarily include exon 19 deletions and the L858R substitution in exon 21, which result in continuous activation of the EGFR signaling pathway, promoting tumor cell proliferation and metastasis.

KRAS mutations are also critical drivers in NSCLC, with a prevalence of approximately 25%, particularly common in adenocarcinoma cases (Zhu et al., 2017; Skoulidis & Heymach, 2019). These mutations mainly occur at codons 12 and 13 and are generally associated with poor prognosis, significantly influencing the biological characteristics of the disease. Additionally, mutations in other driver genes such as ALK, ROS1, and BRAF further contribute to the heterogeneity and complexity of NSCLC, offering new avenues for personalized treatment strategies (Soda et al., 2007; Attili et al., 2024).

Driver gene mutations promote tumor development through various mechanisms. For instance, continuous activation of the EGFR signaling pathway leads to abnormal cell proliferation and survival, disrupts cell cycle regulation, and prevents apoptosis of damaged cells. Understanding these mechanisms provides deeper insights into the biological characteristics of NSCLC and their impact on treatment response (Yang & Fan, 2024).

3. CURRENT STATUS AND UNMET NEEDS IN NSCLC TREATMENT

The current treatment options for NSCLC include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, each with its specific indications and levels of effectiveness. Surgery and radiotherapy are associated with high cure rates in early-stage disease but have limited efficacy for advanced or metastatic NSCLC (Hirsch et al., 2017). Chemotherapy, while a traditional approach that can extend survival, often comes with significant side effects, and patient tolerance and long-term efficacy remain suboptimal (Hirsch et al., 2017).

Targeted therapy has offered new hope, especially for patients with driver gene mutations such as EGFR, ALK, and KRAS (Gainor et al., 2013). EGFR tyrosine kinase inhibitors (TKIs) and ALK inhibitors demonstrate impressive initial effectiveness; however, many patients eventually develop resistance, leading to disease relapse (Mok et al., 2017; Skoulidis et al., 2021). KRAS mutations were historically considered "undruggable," but recent inhibitors targeting KRAS G12C mutations have emerged, although their efficacy is still limited (Leonetti et al., 2018).

Immunotherapy, particularly PD-1/PD-L1 inhibitors, has significantly improved survival for some NSCLC patients. Nevertheless, issues such as resistance and variable patient responsiveness persist (Paz-Ares et al., 2018). Some patients are innately unresponsive to immunotherapy, or they develop secondary resistance over the course of treatment, which severely restricts the effectiveness of these therapies (Rizvi et al., 2015; Rotow & Bivona, 2017). Consequently, NSCLC treatment continues to face considerable challenges, and there is an urgent need for innovative strategies to overcome resistance and enhance therapeutic efficacy (Rotow & Bivona, 2017; Saw & Song, 2019)

4. DESIGN AND MECHANISM OF PEPTIDE DRUGS

Peptide drugs have shown unique advantages in NSCLC treatment, particularly in inhibiting tumor growth and modulating immune responses (Muttenthaler et al., 2021). Compared to small molecule drugs and antibody drugs, peptide drugs exhibit significant differences in binding properties and functionality (Zorzi et al., 2017). Small molecule drugs can penetrate cell membranes and target intracellular sites due to their small molecular weight but often lack targeting selectivity, leading to side effects (Thundimadathil, 2012). Antibody drugs, despite their high specificity, are large molecules that usually cannot penetrate cells and may induce immunogenic reactions (Borrelli et al., 2018). Peptide drugs, with their moderate molecular weight and structural diversity, can flexibly target both cell surface and intracellular targets, have lower immunogenicity, and offer better safety and tolerability (Zhang et al., 2017).

Targeting Epidermal Growth Factor Receptor (EGFR): Peptide drugs can bind to and block EGFR activity, inhibiting tumor cell proliferation and migration. By specifically binding to the EGFR extracellular domain, these peptides inhibit downstream signaling pathways, such as the PI3K/AKT and MAPK pathways, preventing tumor growth (Liu & Kurzrock, 2014).

Inhibiting Vascular Endothelial Growth Factor (VEGF): Certain peptides target VEGF, inhibiting angiogenesis, reducing nutrient supply to tumors, and preventing cancer cell spread and invasion (Liu & Kurzrock, 2014).

Modulating Immune Responses: Peptide drugs can function as immune checkpoint inhibitors, lifting tumor-induced immune suppression, or be designed as peptide vaccines to enhance antitumor immune responses by activating T cells and natural killer cells (Thundimadathil, 2012).

5. APPLICATION STUDIES OF PEPTIDE DRUGS IN NSCLC

In recent years, research on peptide drugs for NSCLC treatment has made significant progress (Muttenthaler et al., 2021). Specifically, in inhibiting tumor growth, peptide drugs have shown potential to prevent tumor spread by targeting receptors and signaling pathways (Saw & Song, 2019). For instance, some peptides targeting EGFR have significantly inhibited tumor cell proliferation (Zhang et al., 2017), while peptides blocking VEGF have reduced tumor angiogenesis (Zhang et al., 2017). Additionally, peptide vaccines and immune checkpoint inhibitors have demonstrated promising roles in modulating immune responses, with some clinical trials validating their potential to enhance immune reactions (Borrelli et al., 2018). However, the practical application of peptide drugs still faces challenges, such as low stability and bioavailability, as well as potential immunogenicity issues (Otvos & Wade, 2014). Nevertheless, some peptide molecules have shown potential to restore tumor cell sensitivity and overcome drug resistance, especially in the context of EGFR mutations (Zorzi et al., 2017). Future research will require more clinical trial evidence to confirm these findings and further optimize the delivery and stability of peptide drugs (Fosgerau & Hoffmann, 2015).

6. ADVANTAGES AND CHALLENGES OF PEPTIDE DRUGS

Peptide drugs exhibit significant advantages in the treatment of non-small cell lung cancer (NSCLC), particularly their precise targeting and low toxicity, surpassing traditional chemotherapy drugs and small molecule inhibitors. Their high selectivity minimizes damage to normal cells, while low immunogenicity reduces systemic side effects, making peptide drugs more suitable for long-term cancer management. However, their clinical application is limited by poor in vivo stability and low bioavailability, which compromise therapeutic efficacy. To address these challenges, researchers are

exploring strategies such as chemical modifications, nano-carriers, and peptide cyclization to extend drug half-life and enhance delivery efficiency.

Despite advancements in the design and optimization of peptide drugs, multiple barriers must be overcome before widespread application is realized. Continued research into innovative delivery strategies and molecular stabilization is necessary to achieve more effective therapeutic outcomes.

7. FUTURE PROSPECTS AND RESEARCH DIRECTION

Peptide drugs have a promising future in NSCLC treatment, especially in the areas of combination therapies and drug design optimization. Future research is expected to focus on the combined use of peptide drugs with existing immunotherapies and other targeted treatments to enhance therapeutic efficacy and overcome the limitations of monotherapies. For instance, peptide drugs could be used in conjunction with immune checkpoint inhibitors to boost anti-tumor immune responses or combined with small molecule inhibitors to target multiple signaling pathways, thereby providing comprehensive suppression of tumor progression. Additionally, peptide drugs could modulate the tumor microenvironment, further promoting the development of combination treatment strategies.

To advance the application of peptide drugs in NSCLC, future research will prioritize further drug design optimization. Leveraging artificial intelligence (AI) and computer-aided drug design (CADD), the structure of peptide drugs can be more precisely refined to improve targeting and efficacy. AI algorithms can analyze vast biological datasets, predict binding patterns between peptides and targets, and rapidly screen efficient and safe peptide candidates. Moreover, advancements in bioengineering and nanotechnology will offer improved solutions for peptide delivery, ensuring stability and efficient delivery in vivo. Overall, through continuous innovation and interdisciplinary collaboration, peptide drugs are expected to play a more significant role in NSCLC treatment, offering more precise and personalized therapeutic options.

8. CONCLUSION

Peptide drugs hold immense potential in the treatment of non-small cell lung cancer (NSCLC), offering exciting new prospects for overcoming the limitations of current therapies. With high selectivity, low toxicity, and structural flexibility, peptide drugs can target critical signaling pathways, modulate immune responses, and overcome drug resistance through various mechanisms, thereby enhancing therapeutic specificity and safety. Studies have shown that peptide drugs have unique advantages in regulating the tumor microenvironment and boosting the efficacy of immunotherapies, demonstrating strongsynergistic effects when used in combination with existing treatments, thus providing breakthrough therapeutic options for NSCLC patients.

Although challenges related to drug stability, bioavailability, and delivery efficiency remain, ongoing technological advancements are paving the way for clinical translation. The development of chemical modifications, nano-carrier systems, and precise delivery techniques is expected to help peptide drugs overcome these obstacles, enabling more effective tumor-targeted therapies. Additionally, by utilizing AI and CADD to optimize drug structures and incorporating new findings from tumor genomics and immunology, the application of peptide drugs in cancer treatment will become increasingly precise and personalized. In summary, peptide drugs not only open new avenues for NSCLC treatment but also hold great promise for the future of cancer therapy as a whole, marking a significant step forward in the era of precision oncology.

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