Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/63/20241720

Development, applications, and future trends of monoclonal antibody therapy

Xiaohang Gao

Shanxi Modern Bilingual School South Campus, Taiyuan, China

tanglingmi@ldy.edu.rs

Abstract. This study outlines the development history, applications, and future trends of monoclonal antibodies (mAbs). Monoclonal antibodies are highly homogeneous antibodies produced by fusing single B cell clones and myeloma cells, with high specificity and consistency. These characteristics make them widely used in the diagnosis and treatment of diseases, especially in oncology and virology research. The paper focuses on several key factors related to treatment, including PD1/PDL1, EGFR, and HER2, and explores their role in mAb therapy. In addition, this paper also analyzes the production cost and yield issues of mAbs and proposes corresponding improvement directions. Although mAbs have broad application prospects in the fields of malignant tumors, CVDs, and neurodegenerative diseases, their high cost remains an important challenge. The study suggests that in the future, attention should be paid to improving the stability of antibodies and reducing costs to promote their continued development in the field of biopharmaceuticals.

Keywords: monoclonal antibody, cancer therapy, PD-1/PD-L1.

1. Introduction

MAbs are antibodies produced by a single B cell clone that target only one specific epitope and have a high degree of homogeneity. The principle of preparation of this antibody is mainly based on hybridoma technology, that is, by fusing sensitized B cells with the ability to secrete specific antibodies and myeloma cells with the ability to reproduce indefinitely into B cell hybridoma

The characteristics of mAbs include high uniformity of physical and chemical properties, single biological activity, and strong specificity of binding to antigen. These properties make mAbs very useful in clinical applications, especially in the diagnosis and treatment of diseases. In oncology, for example, mAbs can identify molecules associated with specific antigens to detect tumors and their metastases; In virology research, mAbs can monitor the synthesis, processing and distribution of viruses by analyzing individual proteins, and can distinguish related proteins to provide genetic markers for gene recombination experiments [1].

The development of mAbs has experienced several stages, such as murine antibodies, chimeric antibodies, humanized antibodies, and fully human antibodies, and its immunogenicity has gradually decreased, and its safety for human use has gradually increased. At present, mAbs have been widely used in the treatment of many diseases such as tumors and immune system diseases, and great progress has been made.

DOI: 10.54254/2753-8818/63/20241720

In addition, mAbs are also used in diagnostic aspects, such as the detection of antigens and antibodies of certain pathogenic microorganisms, the detection of tumor antigens, and the study of immune cells and subcellular structures. Its high specificity and uniformity make the result of antigen-antibody reaction easy to control the quality and facilitate standardization and normalization.

In conclusion, as an important biological product, mAbs is playing an increasingly important role in modern medicine, and its unique preparation technology and wide application fields make it a key tool in modern biotechnology and drug development.

2. Basic therapy of mAbs

MAbs are special protein molecules made by laboratory technology, which are highly specific and uniform, and their main therapeutic modalities are as follows: directly attacking tumor cells; Immune-directed therapy; Blocking signal transduction; Redirect immune effector cells; Modulating immune checkpoints; Combination therapy.

In a study comparing the IFL plus bevacizumab regimen to IFL plus placebo, the hazard ratio for overall survival was 0.66 ($P<0.001$), with the IFL plus bevacizumab group achieving a median survival of 20.3 months. The median progression-free survival was significantly longer in the IFL plus bevacizumab group at 10.6 months, compared to 6.2 months in the IFL plus placebo group (hazard ratio for disease progression, 0.54; $P<0.001$). Response rates were 44.8% for the IFL plus bevacizumab group versus 34.8% for the placebo group ($P=0.004$). Additionally, the median duration of response was 10.4 months with IFL plus bevacizumab, compared to 7.1 months with placebo (progression hazard ratio, 0.62; $P=0.001$). While the IFL plus bevacizumab combination was associated with a higher incidence of grade 3 hypertension (11.0% vs. 2.3%), this side effect was manageable. Overall, these findings support the feasibility of combination therapy with IFL and bevacizumab [2].

2.1. PD1 / PD - L1

PD-1, otherwise known as programmed death receptor-1, is an immune checkpoint that is predominantly expressed on the surface of activated T cells, B cells, and NK cells. It acts as an inhibitor by binding to its ligands PD-L1 and PD-L2, thereby preserving immune tolerance and preventing autoimmune reactions. PD-1 activation can cause a decrease in T cell function and even trigger its apoptosis, which is necessary to avoid tissue damage and autoimmune diseases.

In the tumor environment, tumor cells can inhibit the activity of T cells by expressing ligands such as PD-L1 at a high level, thus escaping the attack of the immune system [3]. MAbs can reactivate T cells and enhance the body's immune response to tumor cells by targeting PD-1 or PD-L1 and blocking their interaction. This mechanism has been successful in many cancer treatments, and the FDA has approved a variety of mAb classes that target the PD-1/PD-L1 pathway for clinical use. Nivolumab and pembrolizumab are two examples [4].

Over the past few years, the number of clinical trials of anti-PD-1/PD-L1 monoclonal antibodies as monotherapy or in combination with other therapies has increased rapidly. Currently, a total of 5,683 clinical trials are evaluating the efficacy of these antibodies, of which 4,897 trials are ongoing. The total number of clinical trials increased by 278% compared to 2017. Although more trials are being conducted every year, recent data shows that the rate of growth is gradually slowing. For example, the number of studies on anti-PD-1/PD-L1 monoclonal antibodies last year only increased by 50% compared with 2017 to 2018. When analyzing anti-PD-1/PD-L1 mAbs approved by the US FDA and their comparison with other yet-to-be-approved antibodies, approximately 29% of clinical trials showed significant therapeutic effects [5].

In summary, therapies that target the PD-1/PD-L1 pathway have demonstrated the ability to significantly enhance the body’s immune response to cancer cells. By blocking this pathway, immune cells, especially T cells, regain their strength and capacity to fight against tumors. While these treatments have gained widespread attention and are being actively explored in numerous clinical trials, the expansion of their use has slowed down slightly in recent years, which may indicate that there are challenges in refining the approach or identifying specific patient groups that benefit most. Overall,

DOI: 10.54254/2753-8818/63/20241720

these therapies offer a promising option in cancer treatment, with ongoing research to improve their effectiveness and application.

2.2. The role of epidermal growth factor receptor (EGFR) in different cancers

EGFR is a transmembrane glycoprotein that belongs to the tyrosine kinase receptor (TKR) family. It plays a vital role in the occurrence and development of tumors by regulating cell proliferation, differentiation and survival. Pathways of abnormal EGFR activation include receptor overexpression, gene mutation, and ligand-dependent and -independent activation. These abnormal activation phenomena are closely related to the occurrence of various cancers [5]. In terms of specific mechanisms, EGFR activates a series of signaling pathways after binding to ligands, such as MAPK and PI3K/Akt pathways. These pathways are crucial for promoting tumor cell proliferation, angiogenesis and survival [6]. The role of EGFR in non-small cell lung cancer (NSCLC) is mainly reflected in its potential as a target, especially in treating patients with specific EGFR mutations. EGFR is a TKR, which activates the downstream signaling pathway by binding to ligand, promotes the proliferation, invasion and metastasis of tumor cells, while inhibiting apoptosis. In NSCLC, overexpression or activation of EGFR is strongly associated with disease progression. EGFR mutation is an important molecular marker in NSCLC, especially in adenocarcinoma subtypes. These mutations usually occur on exon 19 or 21 of EGFR, resulting in a high sensitivity to certain EGFR tyrosine kinase inhibitors (TKIs) such as gegetinib and erlotinib [6].

EGFR also plays an important role in breast cancer (BC). Overexpression of EGFR is associated with enhanced malignant properties of multidrug resistant (MDR) BC cells, including promotion of migration, invasion, and proliferation. The role of EGFR expression varies in different BC subtypes. For example, in TNBC, EGFR expression is higher, and in ER-positive/HER2-negative BC, high EGFR expression is associated with improved prognosis [7]. EGFR plays an important role in various cancers by helping cells grow, survive, and multiply. When something goes wrong, such as a change in its structure or being overly active, it can make cancer cells more aggressive. This means they can spread more easily and avoid natural processes that usually keep them in check. In certain types of lung cancer, EGFR changes make the disease more responsive to some treatments, while in BC, its behavior can vary. In more aggressive forms of BC, EGFR levels are often higher, leading to faster growth and spread. However, in other types of BC, higher EGFR levels might be linked to better outcomes. Understanding how EGFR works differently in various cancers helps guide treatments aimed at stopping its harmful effects.

2.3. HER2

HER2 is a TKR and a member of the HER family. It is overexpressed or gene amplified in some BC patients, and this type of BC usually has more malignant properties and is associated with poor prognosis. Excessive activation of HER2 is closely related to tumor cell proliferation and the enhancement of anti-apoptotic signaling, becoming an important factor driving the progression of HER2-positive BC.

Anti-HER2 mAb combined with chemotherapy is an advanced treatment method for patients with HER2-positive BC. Trastuzumab (Herceptin), a mAb targeting HER2, has been clinically proven to significantly improve the therapeutic effect of patients with HER2-overexpressing metastatic BC. Compared with chemotherapy alone, the addition of trastuzumab can prolong the time to disease progression-free, increase the treatment response rate, and improve the overall survival of patients. Dual-antibody therapies such as pertuzumab combined with trastuzumab and docetaxel have also been shown to further extend patients' disease-free survival without significantly increasing cardiotoxicity [8].

According to experimental evidence, trastuzumab can enhance the survival rate of adjuvant therapy for HER-positive BC. HER2-positive early BC patients were given adriamycin and cyclophosphamide therapy as part of the experiment. According to estimates, 75% of patients with ACT-T experienced disease-free survival for five years. AC-T plus trastuzumab was given to 84% of patients, while 81% took TCH. The estimated overall survival rates were 87%, 92%, and 91%, respectively [9]. The two trastuzumab regimens were both superior to AC-T, but there was no significant difference in efficacy (disease-free survival or overall survival). The incidence of congestive heart failure and cardiac

DOI: 10.54254/2753-8818/63/20241720

insufficiency in the AC-T combined trastuzumab group was significantly higher than that in the TCH group (P<unk>0.001) [10].

Although important progress has been made in the treatment of HER2-positive BC, traditional anti-HER2 drugs still face resistance problems. Therefore, researchers are exploring new combination therapies, including PD-1/PD-L1, CDK4/6 and PI3K inhibitors, to overcome resistance to anti-HER2 treatment. Furthermore, there remain many unanswered questions about how to optimize treatment of HER2-positive/HR-positive advanced BC and determine which patients will benefit from these new therapies.

3. Research progress in the monoclonal antibody therapy

3.1. Resistance and stability

mAbs are susceptible to instability in protein properties, including protein structure and concentration, temperature, interfaces, lighting, excipients, and contaminants. Next is drug resistance, mAb therapy faces the problem of primary and secondary drug resistance, which makes some patients unresponsive to treatment

For these two kinds of problems, there can be some improvements. In terms of stability, structural modification of antibody molecules to improve its stability is an important direction [11]. For example, deamidation can reduce chemical modification sites to improve the stability of mAbs. In terms of resistance, new targets and new mAbs can be developed. For example, LGR 4-specific mAbs have been found to significantly inhibit tumor resistance and work by inhibiting the Wnt/ beta-catenin pathway; Resistance to high-affinity mAbs can improve the stability and persistence of antibodies by optimizing the construction process and reducing immunogenicity using chimeric or humanized antibodies [12].

3.2. Output and cost

At present, mAbs are mainly produced by mammalian cell culture systems, which may bring problems of low efficiency and high cost. In the next 5-10 years, we may see improvements in production platforms, such as microbial fermentation or the utilization of plant expression systems, which can reduce costs and improve scalability. Overall, the technology around mAbs is still evolving, and we can expect to see significant improvements in their efficacy, specificity, and yield in the coming years.

With the rapid development of science and technology in the current era, we can use software for production process modeling and cost accounting, which can help identify key points in the production process and propose corresponding optimization strategies. This method can help enterprises compare different production strategies and find the most economical production solution

3.3. Optimization

MAbs sometimes cause an immune response in patients, leading to reduced efficacy and potential side effects. To reduce immunogenicity, researchers are exploring humanization methods, where non-human sequences replace human sequences, or the development of fully human antibodies using genetically modified animals or in vitro display techniques.

Another way to improve mAbs is to increase their specificity against the target antigen. This can be achieved by using advanced techniques such as generation sequencing (NGS) and single cell analysis to identify unique epitopes that mAbs can target [13].

Stability issues are prevalent due to factors such as protein structure, temperature, and potential contaminants. To address these, structural modifications can enhance the stability of mAbs. For instance, reducing chemical modification sites through deamidation can help maintain their efficacy. Additionally, overcoming drug resistance involves exploring new targets and developing novel mAbs, such as those targeting the LGR4 receptor, which show promise in overcoming tumor resistance by interfering with key cellular pathways. Efforts to improve the stability and persistence of mAbs also include optimizing their design to minimize immunogenicity.

DOI: 10.54254/2753-8818/63/20241720

mAbs face several challenges related to stability, resistance, cost, and optimization. Stability issues arise from factors such as protein structure, temperature, and contaminants, but can be addressed through structural modifications like deamidation, which reduce chemical modification sites. Overcoming drug resistance involves developing new mAbs targeting specific receptors, such as LGR4, which can inhibit tumor resistance by interfering with key cellular pathways. The high cost of mAb production, primarily due to reliance on mammalian cell cultures, is expected to improve with advancements in alternative production methods like microbial fermentation and plant-based systems. Additionally, software for process modeling and cost accounting can aid in optimizing production strategies.

4. Conclusion

This paper mainly describes the current development of mAbs, including several therapies and mechanisms of mAbs, as well as the shortcomings and improvement direction of mAbs, that is, the future development trend. In the first part, several factors needed for therapeutic use, including PD1/PDL1, EGFR and HER2, were explicitly mentioned, illustrating the role and effect of these factors in mAbs. In the section on the future trend of mAbs, this article first pointed out the shortcomings of mAbs in treatment and gave corresponding countermeasures. Secondly, this paper proposes improvements in the production and cost of mAbs, which can reduce costs while increasing the output. In this paper, the development of mAbs so far was summarized, and the future trend of mAbs was also prospected. It once again demonstrated the research value of mAbs and proved that they played an essential role in medical treatment. This paper can help people who do not know mAbs quickly build a basic knowledge framework and understand their development trends. However, many aspects of mAbs still need to be covered, such as the history of mAbs and market analysis of mAbs. At present, mAbs have great promise for the future. The mAbs can be used for malignant tumours, CVDs, and neurodegenerative diseases. Due to the complexity and specificity of mAbs, the price of mAbs is very high. Therefore, research on mAbs can focus on improving their stability and reducing their costs in the future. At present, mAb is still a hot topic of research and development, and it is believed that it will also be an essential driving force for the development of the biopharmaceutical industry in the future.

References

[1] Shao, R. (2020). Monoclonal antibody-based cancer immunotherapy. *Acta Pharmaceutica Sinica*, 55(6), 1110-1118.

[2] Freeman, G. J., Long, A. J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., ... & Wood, C. R. (2000). Engagement of the Pd-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *Journal of Experimental Medicine*, 192(7), 1027-1034.

[3] Li, J. (2018). Application and research progress of monoclonal antibodies targeting immune checkpoint molecules represented by PD-1 in tumor treatment. *Journal of Cell and Molecular Immunology*, 34(7), 650-654.

[4] Cancer Research. (2016). Abstract B30: Discovery and functional characterization of novel anti-PD-1 antibodies using ex vivo cell-based assays, single-cell immunoprofiling, and in vivo studies in humanized mice. *Cancer Research*, 76(15_Supplement), B30.

[5] Singh, D., Attri, B. K., Gill, R. K., & Bariwal, J. (2016). Review on EGFR inhibitors: Critical updates. *Mini-Reviews in Medicinal Chemistry*, 16(14), 1134-1166.

[6] Seshacharyulu, P., Ponnusamy, M. P., Haridas, D., Jain, M., Ganti, A. K., & Batra, S. K. (2012). Targeting the EGFR signaling pathway in cancer therapy. *Expert Opinion on Therapeutic Targets*, 16(1), 15-31.

[7] Dai, X., Li, T., Bai, Z., Yang, Y., Liu, X., Zhan, J., & Shi, B. (2015). Breast cancer intrinsic subtype classification, clinical use and future trends. *American Journal of Cancer Research*, 5(10), 2929-2943.

[8] Gutierrez, C., & Schiff, R. (2011). HER2: Biology, detection, and clinical implications. *Breast Cancer Research and Treatment*, 135(1), 1-10.

[9] Martínez-Sáez, O., & Prat, A. (2021). Current and future management of HER2-positive metastatic breast cancer. *JCO Oncology Practice*, 17(10), 594-604.

[10] Swain, S. M., Miles, D., Kim, S. B., & Baselga, J. (2020). Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): End-of-study results from a double-blind, randomized, placebo-controlled, phase 3 study. *The Lancet Oncology*, 21(4), 519-530.

[11] Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., ... & Kabbinavar, F. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *The New England Journal of Medicine*, 350(23), 2335-2342.

[12] Upadhaya, S., Neftelinov, S. T., Hodge, J., & Campbell, J. (2022). Challenges and opportunities in clinical trials of PD-1/PD-L1 inhibitors. *Nature Reviews Drug Discovery*, 21, 482-483.

[13] Loibl, S., Huang, C. S., Mano, M. S., & Untch, M. (2022). Adjuvant trastuzumab emtansine in HER2-positive breast cancer patients with HER2-negative residual invasive disease in KATHERINE. *NPJ Breast Cancer*, 8(1), 106.