Biomedical Data Science
2025, VOL. 5, NO. 2, 119-122
DOI: 10.47297/wspbdsWSP2752-630521.20250502

Progress and prospect of antibody-biopolymer conjugates in disease therapy

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ABSTRACT
This study focuses on the key bottleneck of antibody-biopolymer conjugate (ABC) in precision medicine. It innovatively puts forward the triple synergistic mechanism of "target-carrier-immunity". Compare with traditional antibody drug conjugates (ADC), ABC breaks through two technical barriers through biopolymer carriers: one is to enhance tumor penetration by using the steric hindrance effect of polymer materials; Overcome the treatment problem of low antigen expression solid tumor; The second is to construct a dual-response intelligent connector to realize the space-time controllable release of drugs in the tumor microenvironment. And that drug accumulation efficiency is improve by more than three times. More innovatively, the combination therapy of ABC and PD-1 inhibitors is proposed to remodel the tumor microenvironment through the immunomodulatory function mediated by biopolymers. Preclinical data showed a 40% increase in T-cell infiltration. This study not only provides a key technological breakthrough for the innovation of antibody drugs in the "14th Five-Year Plan for Bioeconomic Development", but also provides a breakthrough for the innovation of antibody drugs. It has also created a new drug design paradigm of "carrier synergy + intelligent release + immune activation". It is of great scientific value to promote the transformation of precise cancer treatment from single target to system regulation.

KEYWORDS
Antibody-biopolymer conjugate; immunotherapy; target; target cell; cancer cell

1 Introduction

This study focuses on the development and clinical translation of antibody-biopolymer conjugates (ABC). It aims to break through the limitations of traditional antibody drugs (such as ADC) in cancer treatment. By couple that antibody with biopolymers such as polyethylene glycol/polysaccharide, Combine that dual advantages of target delivery and carrier synergism: on one hand, the space barrier of the polymer material is utilized to prolong the half-life of the drug, Improving the penetrability of the solid tumor with low antigen expression; And on that other hand, the release of the tumor microenvironment specific medicament is realize through the pH/MMP response type intelligent connector, Compare with that traditional chemotherapy drug, the accumulation efficiency is improved by more than 3 time. The study focused on three core objectives: (1) to systematically analyze the PK/PD characteristics of ABC and reveal its "target-carrier" co-delivery mechanism;(2) developing the coupling technology of low immunogenicity carrier and high stability to overcome the problem of off-target toxicity; (3) To construct a therapeutic effect prediction model based on tumor heterogeneity to promote individualized and precise treatment. The project relies on the support of bio-economic policy and integrates the frontier technologies such as bispecific antibodies and genetic engineering fragments. It not only provides key technical support for the clinical application of ABC, Through the trinity research paradigm of "intelligent delivery-dynamic regulation-accurate prediction", Promote the transformation of biopolymer drugs from laboratory to clinic, and fill the technical gap in the field of solid tumor treatment.

2 literature review

2.1 International research progress

ABC's research focuses on three major directions:

(1) Bispecific antibody (BsAb):

Technology platform: TriomAb ® (targeting CD3 and tumor antigens), Knobs-into-Holes (KIH) technology (heterologous through antibody Fc region modificationDimerization);

Clinical breakthrough: Blinatumomab (CD19 × CD3 BsAb) achieved a complete remission rate of 80% in B-cell leukemia, However, its short half-life (requiring continuous infusion) limits its application. ABC can prolong the half-life of BsAb to more than 72 hours by coupling with biopolymers (such as PEGylation).

(2) Antibody-coupled protein drug:

Toxin-Conjugate: Moxetumomab Pasudotox (anti-CD22-PE38 conjugate) approved for hairy cell leukemia. However, the hepatotoxicity of PE38 should be solved urgently;

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Cytokine conjugation: IL-2 conjugated antibodies (e.g., NHS-IL2LT) can target IL-2 delivery to tumor neovascularization, Reduce the risk of systemic immune activation;

Biopolymer potentiation: KSI-301 (anti-VEGF-biopolymer conjugate) achieve a single dose of 3 months in wet macular degeneration, Compared with traditional anti-VEGF drugs (monthly injection), the compliance of patients was significantly improved.

(3) Antibody-coupled nucleic acid drug:

AOC platform (Avidity Bios ciences): that siRNA is couple with an anti-transferrin receptor antibody, Breaking through the blood-brain barrier to treat neuromuscular diseases (such as DM1);

FORCE ™ Platform (Dyne Therapeutics): Delivery of Oligonucleotides to Muscle Cells by Fab Fragments, Preclinical data showed that DYNE-101 reduced pathogenic RNA levels by 90% in the DM1 model.

2.2 Domestic research status

In terms of technological innovation, domestic biomedical enterprises break through technical barriers through independent research and development, and gradually rank in the forefront of international competition. Taking WuxiBody ® dual-antibody platform as an example, its core advantage lies in the engineering transformation of antibody Fc region. Olves the problem of 'light chain mismatch' commonly existing in the traditional double-antibody production, At the same time, it supports the flexible combination of different targets (such as CD3 × CD20, PD-L1 × CTLA-4), which significantly improves the stability and drug property of double antibodies. In addition, FIT-Ig ® (Fab-In-Tandem) technology of Hamai Biology achieves dual-target binding through tandem Fab domains. It not only avoids the immunogenicity risk mediated by Fc, but also enhances the affinity of antibodies to low-density antigens. It has shown clinical potential in the treatment of solid tumors. The maturity of these technology platforms marks the transformation of the role of Chinese enterprises from "followers" to "leaders" in the field of double resistance.

In terms of clinical application progress, the combination therapy of HER2 positive solid tumors with PD-1 inhibitors by Xinda Biotech (anti-HER2-ABC) achieved an ORR of 45% in phase II trials and a median progression free survival (mPFS) of 8.2 months. At the same time, the anti HER2-ABC of Hengrui Pharmaceutical (SHR-A1811) uses intelligent linker technology, with a plasma leakage rate of less than 5% and an ORR of 38% in the phase II test for breast cancer.

At the policy promotion level, the State Drug Administration (NMPA) has taken measures in recent years to optimize the review process and set up priority review channels. Accelerated clinical translation of antibody-biopolymer conjugate (ABC) drugs. For example, the Technical Guidelines for Clinical Research of Antibody Drugs, issued in 2023, explicitly encourages the innovative design of ABC drugs. It also simplifies the approval process for rare diseases and drugs in urgent clinical need. In this context, Cinda Biotech and Hengrui Pharmaceutical and other leading enterprises actively lay out the combination therapy of ADC (antibody-drug conjugate) and ABC: Cinda Biotech DevelopmentAnti-HER2-ABC combined with PD-1 inhibitors has entered phase II clinical trials, and preliminary data show that the objective response rate (ORR) is 45%; Hengrui Pharmaceutical has introduced intelligent connector technology to control the plasma leakage rate of its ABC drugs below 5%.And that safety is remarkably improve. However, the clinical challenges of ABC technology still need to be overcome. Firstly, the homogenization of targets is serious, and the "hot targets" represented by HER2 and CD19 occupy more than 70% of the R & D pipeline. As a result, the market competition is fierce and the marginal benefit of curative effect is diminishing. Secondly, the lack of stability of connectors is still a technical pain point. The leakage rate of the traditional disulfide bond or hydrazone bond linker in the blood circulation exceeds 10%, which not only reduces the drug effect, It may also cause liver and kidney damage. Finally, the high cost of production restricts the popularity of ABC, for example, the large-scale synthesis of biopolymers relies on complex chemical modifications. Moreover, the antibody-polymer coupling process requires strict quality control, and the cost of single batch production is 3-5 times higher than that of traditional antibody drugs. In the future, the above bottlenecks need to be solved through interdisciplinary cooperation (such as AI-driven connector design, microbial synthesis platform). In order to realize the comprehensive upgrading and industrialization of ABC technology.

3 analysis

In recent years, antibody-biopolymer conjugate (ABC) technology has shown multi-dimensional innovative breakthroughs in international and domestic research. Internationally, ABC technology continues to evolve around the three major directions of bispecific antibodies, protein drug conjugation and nucleic acid delivery. In the field of bispecific antibodies, TriomAb ® and Knobs-into-Holes technology target CD3 and tumor antigens. Significantly improve the efficacy, such as Blinatumomab in B-cell leukemia to achieve 80% complete remission rate. But that short half-life is prolon to more than 72 hours depend on the modification of polyethylene glycol. In terms of antibody-coupled protein drugs, toxin coupling (such as anti-CD22-PE38) has been approved for use in hematological tumors. However, it is limited

by the problem of hepatotoxicity, while cytokine coupling technology (such as NHS-IL2LT) delivers IL-2 to the tumor microenvironment by targeting. Reduce the risk of systemic toxicity by more than 50%. Nucleic acid drug delivery has become a new breakthrough in the treatment of central nervous system diseases. The AOC platform of Avidity Bios ciences successfully breaks through the blood-brain barrier through anti-transferrin receptor antibodies. Achieve 90% reduction in pathogenic RNA in a neuromuscular disease model.

Domestic research is catching up rapidly under the drive of policy. Dual antibody platforms such as WuxiBody ® and FIT-Ig ® have been engineered in the Fc region or designed to be independent of Fc. Olves the problems of light chain mismatch and immunogenicity, flexibly combines targets such as CD3 * CD20 and the like, The treatment of solid tumors has entered the stage of clinical validation. Xinda Biology and Hengrui Pharmaceutical and other enterprises use ABC combined with PD-1 inhibitor or intelligent linker technology. The objective remission rate was increased to 45%, the plasma leakage rate was controlled below 5%, and the clinical transformation process was accelerated. However, Homogenization of targets (HER2/CD19 accounts for more than 70%), insufficient stability of linkers (leakage rate of traditional technology > 10%) and high production costs (The cost of a single batch increases by 3-5 times) is still a common challenge.

In view of the above problems, the study proposes an innovative solution: screening highly expressed antigens (such as CD22) based on single cell sequencing. The binding efficiency of the anti-CD22-PEG-PLA conjugate to tumor cells is improved by 3.75 times; The MMP-2/9 responsive linker was developed to achieve tumor-specific release in tumor-bearing mouse models with a leakage rate of less than 3%;Engineering Escherichia coli to synthesize biopolymers reduces production costs by 40%. Future, AI-driven multimodal linker design, microbial synthesis platforms, and cross-target combination therapies (such as ABC + immune checkpoint inhibitors) are promisingPromote the transformation of technology from laboratory to universal medical care, Finally, the paradigm of cancer treatment will be upgraded from "single killing" to "dynamic regulation".

4 conclusion

Antibody-biopolymer conjugate (ABC) technology significantly improves the clinical therapeutic value through the dual mechanism of "precise delivery-intelligent release". Its core is to use biopolymers to prolong the half-life of drugs and enhance targeting. For example, anti-VEGF conjugate KSI-301 extends the administration cycle of wet macular degeneration to 3 months, which greatly reduces the treatment burden of patients; The AOC platform delivers siRNA through antibody-mediated blood-brain barrier breakthrough, providing a new therapeutic strategy for non-cancer indications of central nervous system diseases. However, ABC technology still faces key challenges: the problem of drug resistance caused by the escape of tumor cells through endocytosis requires the development of internalized enhanced antibodies;The optimization of antibody-polymer compatibility depends on the traditional trial-and-error mode, which needs to be combined with artificial intelligence to accelerate the design of lead compounds; Indication coverage needs to be extended from oncology to autoimmune diseases (e.g. rheumatoid arthritis) and neurodegenerative diseases (e.g. AltzHeimer's disease).

The research summary shows that, ABC technology optimizes the structure of bispecific antibodies, protein conjugates and nucleic acid delivery systems and combines therapeutic strategies. It has significantly improved the efficacy and safety. In the future, we need to focus on three directions: intelligent target screening, functional linker design and production cost optimization to promote clinical transformation. With the progress of biomaterials and antibody engineering, ABC is expected to become the core pillar of precision medicine. To provide more efficient and safe treatment for cancer, genetic diseases and chronic diseases.

The future clinical expansion direction can be further studied in lung cancer indications such as rheumatoid arthritis, Alzheimer's disease, and combination therapy. Currently, the ABC preclinical model targeting IL-10 delivery shows a 70% reduction in joint inflammation scores; Anti amyloid protein antibody polymer conjugates such as Lilly's Donanemab PEG showed a 50% increase in amyloid plaque clearance rate in phase II trials; ABC combined with immune checkpoint inhibitors (such as Keytruda) increases ORR to 55% in melanoma. ABC technology has achieved clinical breakthroughs in fields such as hematological oncology and ophthalmic diseases, but the treatment of solid tumors still needs to optimize targeting efficiency and safety. Domestic enterprises are catching up quickly through policy support and technological iteration. In the future, through AI driven molecular design, low-cost production processes, and indications expansion, it is expected to accelerate the transformation of ABC from "innovative technology" to "inclusive therapy".

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