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The Development Process and Characteristics of Antibodies in Antibody-drug Conjugate

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Abstract. More than 100 years ago, Paul Ehrlich, the father of immunology, first proposed the concept of "magic bullets", i.e., the concept of selectively delivering toxic drugs to target cells while avoiding damage to normal cells in the human body. ADCs, as a new type of anticancer drug, are formed by coupling small molecule cytotoxins with monoclonal antibody molecules through linker molecules. As a new type of anticancer drug, ADC couples a small molecule cytotoxin with a monoclonal antibody molecule through a linker molecule, and the drug formed by the combination is targeted and lethal, leading the new era of targeted cancer therapy. In this review, the current development and outlook of ADCs is comprehensively reviewed, ADCs and ongoing R&D pipelines in the global and Chinese markets are analyzed,Various ADC platforms and technologies pertinent to distinct pharmaceutical and biotech firms are emphasized, alongside an exploration of emerging technologies, potential advancements for next-generation ADCs, and avenues for clinical research.

Keywords: Antibody drug, linker, payload, ADCs, Clinical progress.

1. Introduction

Progress in biopharmaceutical technology has facilitated the creation of antibody-drug conjugates (ADCs), a groundbreaking category of anticancer therapies, heralding a new epoch in cancer treatment with significant accomplishments [1]. An ADC comprises an antibody, a potent cytotoxic drug molecule (payload), and a linker that connects the two components. ADCs function as a hybrid of targeted and chemotherapeutic agents by precisely identifying the target antigen through the antibody and delivering the cytotoxic payload to eradicate the target cells. The diminutive molecules of specific antibody-drug conjugates (ADCs) can infiltrate the cell membrane, consequently inducing apoptosis in adjacent tumor cells, a phenomenon referred to as the bystander effect. Moreover, specific antibody-drug conjugates (ADCs) exhibit antibody-immunizing effects, including complement-dependent cytotoxicity (CDC), antibody-dependent cytotoxicity (ADCC), and antibody-dependent cell phagocytosis (ADCP) [2].

Antibody-drug conjugates (ADCs) are frequently administered with the following chemotherapeutic agents. Conventional antibodies function by obstructing specific signaling pathways or physiological mechanisms that facilitate tumor proliferation. In the domain of antibody-drug conjugates (ADCs), the binding of the antibody to the target antigen on malignant cells enables the cytotoxic payload to exert its anti-tumor effect by either directly inhibiting tumor cell mitosis or disrupting the DNA structure. Consequently, the theoretical lethality efficacy of antibody-drug conjugates surpasses that of

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conventional antibodies. Furthermore, owing to their target selectivity, ADCs exhibit reduced systemic toxicity compared to traditional chemotherapeutic agents, thereby offering an improved safety profile [3]. Secondly, for patients exhibiting resistance to current targeted therapies, antibody-drug conjugates (ADCs) that target the same receptors may remain effective, thereby broadening their application in cancer treatment [4]. The human epidermal growth factor receptor 2 (HER2) is a significant target in breast carcinoma. Patients with metastatic breast cancer resistant to anti-HER2 therapy may still experience prolonged benefits from the anti-HER2 antibody-drug conjugate Trastuzumab Deruxtecan (Enhertu, DS-8201). Enhertu demonstrated efficacy in breast cancer patients exhibiting low HER2 expression via the bystander effect, thereby redefining the classification of HER2-positive breast cancer. Antibody-drug conjugates (ADCs) can precisely target novel therapeutic sites [5,6].

The concept of drug coupling originated from Paul Ehrlich's "magic bullet" theory in 1913, requiring almost 90 years of enhancement, formulation, and technological advancement prior to the launch of the first antibody-drug conjugate, Gemtuzumab Ozogamicin (Mylotarg), for clinical use [7]. At present, 15 antibody-drug conjugates (ADCs) have received approval, and over 200 have undergone evaluation in clinical trials [8]. Antibody-drug conjugates (ADCs) have emerged as one of the most rapidly expanding categories of anticancer treatments in the last ten years. The advent of ADCs represents a significant advancement, yet it introduces new challenges related to the design and integration of their various components for optimal performance. The in vivo effects and metabolic processes indicate that variations in target selection, drug structure, recognition site, and linker type can result in substantial differences in pharmacological efficacy, toxicity, pharmacokinetics, and controlled release [9]. These characteristics present significant challenges for chemical manufacturing and control (CMC), pre-clinical studies, and subsequent clinical trials. Consequently, antibody design, linker technology, payload and ligation techniques, have become pivotal challenges in the development of ADCs [10].

2. Selection of Antibodies in ADC Drugs

ADC drug antibodies need to have high antigen affinity and a long circulating half-life, which can be specifically enriched at the tumor site. The types of antibodies used to develop ADC drugs are mainly IgG sub-types, which gradually shift from early lgG4 to lgG1 [11]. At present, the selection of antibodies is mainly humanized antibodies, which have low immunogenicity, high specificity and high affinity. According to the half-life, conjugation convenience, structural stability, and immune function of Fc fragments for different IgG isoforms, the IgG1 isoform was mostly selected for antibodies [12].

2.1. Characteristics of Antibodies

The optimal antibody for application in an ADC must exhibit a robust affinity for target binding. It possesses good stability, minimal immunogenicity, effective internalization, and an extended plasma half-life [13]. The high specificity of antibody molecules is crucial for the success of antibody-drug conjugates, with IgG1 being the predominant subtype utilized. Upon selecting the target antigen, it is essential for the antibody to bind selectively to the antigen for accurate guiding; thus, the antibody's high targeting capability and potential immunogenicity must be evaluated [14].

2.1.1. Low immunogenicity

According to the immunogenicity of antibodies, they can be divided into fully humanized antibodies, humanized antibodies, and chimeric antibodies, and more humanized or fully humanized antibodies can be selected to reduce immune response [15]. Immunogenicity is primarily related to the source of the antibody. At the beginning of the development of ADC drugs, murine antibodies were still mainly used, and the strong immunogenicity led to greater side effects and a high failure rate of research and development. With the technological progress of protein engineering and genetic engineering, antibodies are gradually developing in the direction of humanization, and the immunogenicity continues to decrease. At present, it has been able to achieve full humanization, which has improved the efficiency of ADC drug research and development. For the marketed ADCs, only Adcetris uses chimeric antibodies, while other marketed drugs and most ADCs currently in development use humanized or

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human monoclonal antibodies [16]. There are 4 main categories of therapeutic antibodies based on their source.

The first generation of ADCs

Rodents: problems with immunogenicity, short half-life, and limited penetration at tumor sites

Chimerism: Reduced immunogenicity and extended half-life compared to murine monoclonal antibodies

Second-generation ADCs

Humanized: Reduced immunogenicity compared to chimeric monoclonal antibodies

Third-generation ADCs

Fully humanized: Significantly reduced immunogenicity compared to humanized monoclonal antibodies

2.1.2. Long half-life

The Fc fragment of the antibody can be enhanced or attenuated to modulate the intensity of the immune response mediated, which can also affect its stability and half-life [17]. ADC drugs predominantly utilize the IgG1 molecule within the humanized monoclonal antibody subtype, which offers a high affinity for the target antigen, an extended half-life in circulation, and numerous natural conjugation sites, comprising 60-70% of plasma, significantly surpassing other subtypes [18]. Advancements in technology have facilitated the utilization of IgG4 in the research and development of ADC medicines; nonetheless, IgG4 is less prevalent in plasma, exhibits reduced structural stability compared to IgG1, and is prone to aggregation at low pH levels. Given that various isoforms of IgG has distinct functions, future research and development may concentrate on selecting different isoforms of heavy and light chains for recombination to produce novel monoclonal antibodies. Konitzer et al. reconstructed the IgG2 or IgG4 heavy chain in place of the IgG1 heavy chain, resulting in a more stable profile for the combined antibody [19].

2.1.3. High affinity

The effectiveness of antibody internalization is mostly associated with the antibody's affinity for the antigen. Increased affinity of antibodies utilized in the ADC enhances internalization efficiency; however, antibodies with excessively high antigen affinity diminish the penetration efficiency of solid tumors, thereby impacting the ADC drug's ability to reach the tumor interior [20]. Consequently, antigens must be identified and attached by antibodies with an adequate affinity ($Kd \leq 10$ nM) to guarantee fast uptake in target cells [21]. Take into account the molecular weight of the chosen antibody; if the molecular weight is excessively high, it may struggle to traverse the capillary endothelium layer and extracellular space, whereas a molecular weight that is too low could compromise its in vivo half-life. The primary focus of ADC antibody optimization is to enhance endocytosis and osmotic efficacy. The primary hurdles for antibody-drug conjugates (ADCs) are insufficient efficacy and off-target toxicity, largely due to the low number of ADCs that reach the tumor and the restricted rate of internalization [22].

2.2. Target Selection

Appropriate targets markedly affect the pharmacological properties of ADCs. The target antigens of approved antibody-drug conjugates (ADCs) are specific proteins that are overexpressed in common tumor cells, such as HER2, TROP2, and Nectin4 in solid tumors, and CD19, CD22, CD33, and CD30 in hematological malignancies.[23] Recently, the progress of new ADC targets has been robust, and the techniques for selecting target antigens are consistently being improved. A promising strategy entails the identification of mutant proteins in tumors, which generally display increased levels of ubiquitination modifications and are more easily internalized and degraded than wild-type proteins [24]. Targeting antibody-drug conjugates (ADCs) containing oncogenic mutant proteins can improve therapeutic specificity. Recent advancements in fundamental tumor immunology research have expanded the target development of antibody-drug conjugates (ADCs) from traditional tumor antigens

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to encompass microenvironmental and cancer stem cell antigens[25]. An increasing number of ADCs based on this principle may enter preclinical and clinical trials in the future. Furthermore, the recognition of these new targets will greatly expand the applications for future ADC therapeutics [26].

2.3. Future Development of Antibodies in ADCs

Numerous technology platforms focus on enhancing ADC antibodies, with prospective advancements involving the selection of antibody serotypes, augmentation of antibody humanization, and modification and optimization of antibody structures. Recent proposals for antibody-drug conjugate (ADC) design include conditional antibody ADCs, bispecific ADCs, non-internalized ADCs, and the substitution of antibody vectors with alternative molecular types, which will shape the future trajectory of ADC development [27]. Researchers are presently devising methods to enhance delivery efficiency and internalization speed, including improving penetration and using ADC medicines with bispecific antibodies [28].

2.3.1. Use Bispecific antibodies to enhance affinity and specificity

Bispecific antibodies can concurrently bind to two antigens on a single target cell, a characteristic that may enhance the therapeutic window while minimizing off-target effects on non-target cells [29]. Moreover, employing bispecific antibodies that target two distinct epitope antigens can augment the antibody's affinity for the antigen, thereby enhancing the endocytosis efficiency of the ADC medication [30].

2.3.2. Remove the Fc end to improve permeability

Due to their substantial size, ADC therapeutics must surmount the stromal barrier and penetrate tumor tissue when addressing solid tumors. The current technique primarily aims to reduce the molecular weight of the antibody, as it constitutes a substantial portion of the structure [31]. For instance, scFv (single-chain variable fragment) or sdAb (single-domain antibody) serve as foundational components for antibody production; due to their low molecular weight, the resultant antibodies are smaller than IgG and can penetrate tumors more rapidly [32].

2.3.3. Bystander effect to resolve binding site barriers

A contributing factor to inadequate tumor permeability may be the binding site barrier effect [33]. This phenomenon occurs when antibodies with high affinity for target antigens adjacent to blood arteries exhibit diminished distribution away from these vessels due to the quick and strong binding of antigens, leading to decreased tumor clearance efficacy of antibody-drug conjugates (ADCs). Small-sized ADCs that enhance permeability and dispersion can utilize the "bystander effect" to eliminate neighboring tumor cells and overcome site barriers [34].

3. Current Status of Antibody Development for ADC Drugs

In 1975, Kohler and Milstein developed hybridoma technique and produced the first generation of monoclonal antibodies, namely murine monoclonal antibodies, marking the commencement of a new era in monoclonal antibody research [35]. In clinical treatment, murine monoclonal antibodies exhibit significant immunogenicity, resulting in the production of human anti-mouse antibody (HAMA) reactions. With advancements in antibody preparation technology, the development of monoclonal antibodies has evolved from murine antibodies to human-mouse chimeric antibodies, humanized antibodies, and ultimately fully human antibodies, thereby substantially reducing immunogenicity and enhancing the efficacy of monoclonal antibodies [36]. The immunogenicity of antibodies has significantly diminished, while the safety and efficacy of monoclonal antibodies have been enhanced. In recent years, the swift advancement of humanized and completely human antibodies, characterized by low rejection rates and extended blood half-lives, has emerged as a predominant trend in antibody drug development, comprising over 80% of newly authorized antibody therapeutics by the FDA [37,38].

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Currently, the majority of global ADC medicines are created with these antibodies.Monoclonal antibodies utilized as ADC carriers are enumerated below based on the target molecules they identify:

3.1. Antibody drugs targeting HER2

3.1.1. Trastuzumab

Trastuzumab (Herceptin) is an antibody therapy that specifically targets HER2. Hereeptin is a recombinant humanized IgG1 monoclonal antibody targeting HER2. Trastuzumab (Herceptin) is a recombinant humanized anti-HER2 IgG1 monoclonal antibody that received FDA approval in 1998 for the treatment of metastatic breast cancer [39]. In 1998, the FDA sanctioned Hereeptin for the treatment of metastatic breast cancer, establishing it as the inaugural antibody drug approved for oncological therapy. In 2006 and 2010, the FDA sanctioned patulin for the management of postoperative early breast cancer, metastatic gastric cancer, and esophagogastric junction cancer, respectively [40].

3.1.2. Pertuzumab

Pertuzumab (Peb) is a fully recombinant humanized anti-HER2 IgG1 monoclonal antibody. It attaches to domain II of the extracellular region of the HER2 receptor, inhibiting HER2 homo- or heterodimerization. Formation of homo- or heterodimers and the inhibition of downstream signaling pathways [41]. In June 2012, the FDA sanctioned pertuzumab for the treatment of HER2-positive advanced or metastatic breast cancer [42].

3.2. Antibody Drugs Targeting EGFR

3.2.1. Cetuximab

Cetuximab (Erbitux) is a chimeric IgG1 monoclonal antibody that antagonizes endogenous ligands by binding to the extracellular domains of the epidermal growth factor receptor (EGFR). competes with endogenous ligands for binding to the extracellular domain of the EGFR. Cetuximab obtained FDA marketing authorization in 2004 [43]. FDA-approved for the treatment of metastatic colorectal cancer and head and neck squamous cell carcinoma [44].

3.3. Antibody drugs targeting CD20

3.3.1. Rituximab

Rituximab (Rituxan) is a chimeric monoclonal antibody, integrating human and murine components, that specifically targets CD20. In 1997, it obtained U.S. FDA approval for the treatment of B-cell non-Hodgkin's lymphoma, establishing it as the inaugural monoclonal antibody authorized for clinical application by the FDA [45]. In 2010, the European Commission approved it for the maintenance treatment of follicular lymphoma after initial therapy. Moreover, it has been widely employed in the treatment of systemic lupus erythematosus, idiopathic thrombocytopenic purpura, chronic lymphocytic leukemia, multiple myeloma, and autoimmune pancreatitis. [46].

3.3.2. Teimumab

Tibritumomab (ibritumomab, Zevalin) is the first radio-labeled monoclonal antibody in the world. It is a radioisotope-labeled anti-CD20 IgG1 monoclonal antibody, approved for use in the United States in 2002 for the treatment of refractory relapsed B-cell non-Hodgkin's lymphoma. [47].

4. Conclusion and Prospect

Antibody-drug conjugates (ADCs) combine the high specificity of antibodies with the powerful tumor-killing properties of cytotoxic agents, becoming a central focus in anti-tumor antibody research and development. Antibodies, functioning as the carriers for ADC therapeutics, are essential factors in the development of effective ADCs. The development of monoclonal antibodies has advanced through several stages: murine, human-mouse chimeric, humanized, and fully human antibodies. The

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immunogenicity of monoclonal antibodies has progressively diminished, while their blood half-life has steadily grown, establishing a basis for the advancement of optimal ADC therapeutics. In the advancement of next-generation antibody-drug conjugates, it is essential to evaluate and enhance the target, affinity, immunogenicity, relative molecular mass, and efficacy of the antibody. Furthermore, there is a continuous need to identify novel effective antibody targets and to engineer more potent, smaller relative molecular mass, and more permeable antibodies or antibody fragments for the development of optimized ADC therapeutics.

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