Dean&Francis

ISSN 2959-409X

Discussion on solving drug-resistant issues using antibody-based drugs

Zerui Liu [1*]

[1]*New Channel Shenzhen School, Shenzhen, Guangdong, China*
**Corresponding author: Liuzr13691715075@outlook.com*

Abstract:

As the problem of drug resistance increases, which dramatically threatens current therapies, all public health-related agencies are trying to find potential solutions to these issues. Most efforts are focused on the drugs themselves, searching for alternative substances with different actions and mechanisms to inhibit or kill resistant pathogens. However, it may be beneficial to approach the problem from a different perspective. Antibodies, a type of polypeptide usually produced during the adaptive immune response, have begun to show considerable potential in solving these problems. Currently, antibody-conjugate drugs have shown excellent results in the treatment of cancers and, in some cases, viral infections. Thus, the hypothesis has been proposed that using antibodies or antibody-based drugs could treat diseases such as common bacterial or viral infections. Therefore, this may provide alternative approaches for solving these problems.

Keywords: Antibody-Drug Conjugates (ADCs); Antimicrobial Resistance; Monoclonal Antibodies; Targeted Therapy ; Alternative Therapeutics

1 Introduction

Since the discovery of penicillin, antibiotics have saved countless lives from bacterial infections. However, antimicrobial resistance has increased sharply over the past eight decades, with multidrug-resistant strains posing major challenges to treatment due to the scarcity of new antimicrobial drugs [1,2]. Bacteria readily acquire drug resistance through selection pressure, similar to natural selection. Random mutations during bacterial replication, which may change bacteria metabolism, such as the intracellular antibiotic concentration, modifying of the antibiotic target, or inactivating the antibiotic, which could help the bacteria surviving under antibiotics treatments [3]. Consequently, the resistant bacteria can transmit their advantageous genome, leading to the dominance of resistant strains. Similarly, viruses have mechanisms to evade anti-viral drugs. while the pace of new drug development lags behind pathogen mutation, leading to the shortage of effective therapies.

Antibody drugs often referred to the antibody-drug conjugates (ADCs), which are immunoconjugates that combine the specificity of monoclonal antibodies with a cytotoxic agent [4]. These antibodies, connected to cytotoxic molecules through chemical linkers, selectively bind to antigens on disease cells, enabling targeted delivery of the cytotoxic payload

and inducing apoptosis. Compared with traditional chemical molecules used in antibiotics and antiviral drugs, some particular antibodies can more easily reach efficient cellular internalization, immunogenicity, and have a longer blood plasma half-life [5]. Currently, ADCs are primarily applied in oncology due to their specific targeting capacity and potent cytotoxicity [6]. Furthermore, the relevant characteristics also indicate the potential for treating other diseases, such as bacterial or viral infections.

2 Current drug therapeutics and their limitation

Since the discovery of the first antibiotic, the rapid emergence of antimicrobial resistance has led to rising mortality, making the search for effective solutions an urgent global task. Antibiotics, classically define as compounds produced by microorganisms or plants, serve diverse ecological roles, including defense, predation, signaling, and host interactions [7-9]. Current antibiotics are typically derived from active components of target bacteria, which are often cultivated to enhance the output

2.1 Mechanisms of antibiotic action

Antibiotics exert their effects through several mechanisms. One major mechanism involves inhibition of bacterial DNA replication: a particular type of antibiotic known as fluoroquinolone antibiotics can inhibit the function of topoisomerase IV, which can prevent the formation of new bacterial DNA [10,11]. The other mechanism is inhibition of ribosomal function. Like other organisms, bacteria use DNA coding for the sequence of amino acids, which means they also have the processes of protein biosynthesis. Protein synthesis in bacteria takes place on a type of organelle called a ribosome, which is made up of 50S and 30S subunits [12]. Therefore, antibodies can target the subunits of the ribosome or the enzymes involved in protein synthesis [13]. For instance, the aminoglycoside antibiotics, which can enter the bacterial cells due to their positive charge, inhibit the functions of the 30S subunit [14,15]. Additional mechanisms include inhibition of cell wall synthesis and folate metabolism [12].

2.2 Antibiotics resistance: Genetic foundations and public health impact

Antibiotic resistance has emerged as a major global health threat by the World Health Organization [16]. There are two main genetic mechanisms of resistance: mutational resistance and horizontal gene transfer (HGT) [16]. Random mutation may enhance bacterial survival capacity in the presence of antibiotics, enabling resistant strains to predominate. In parallel, mobile genetic elements (MGEs) such as plasmids and transposons facilitate intercellular transfer of resistance genes, accelerating their spread within and across species [16,17]. The mutated genes usually allow bacteria to escape from antibiotics by reducing the intracellular drug accumulation, modifying targets of antibiotics such as DNA gyrase or topoisomerase, protecting the ribosome, or producing inactivating enzymes [10]. In addition, the development of new antimicrobial agents is slow, costly, resource-intensive, and restricted by numerous testing and regulatory requirements, placing humans at a disadvantage in the evolutionary race against resistant pathogens.

2.3 Existing and possible solutions

The discovery of new antibiotics remains essential approach, though it faces significant challenges. The usage of antibiotics needs to be supervised and restricted strictly to prevent the abuse of antibiotics. Treatment strategies also play a critical role, as it affects both therapeutic efficacy and mutation rates. For example, tuberculosis therapy includes several types of antibiotics and a relatively long period of time. The combination of drugs involves Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol, which can prevent the survival of potential resistant bacteria and complete elimination of bacteria [18].

2.4 Anti-viral drug

Anti-viral drugs also face similar problems, which provide some severe conditions to public health. In conclusion, it becomes particularly important to find alternative solutions.

3 Antibody-based drug

The antibodies are a kind of specific glycoprotein, which consist of two pairs of polypeptide chains and have a basic structure of a flexible Y shape [19]. The stem of the Y consists of two identical heavy chains, while each arm is composed of a smaller protein, which is called a light chain, and the two light chains are also identical [19]. The stem and the bottom of the arms of some particular classes of antibodies are very similar, which is called the constant region [19]. The tip of each arm of the Y-shaped molecule is an area called the antigen-binding, or antibody-combining site. Apparently, this site has the corresponding shape to the epitope on the antigens, which can bind with the antigens effectively, forming a chemical bond [20].

Antibody are mainly grouped into five classes base on the structure of them of constant region, including: IgG, IgM, IgA, IgD, and IgE [19]. Ig refer to the abbreviation of the

ISSN 2959-409X

word immunoglobulin [19]. In addition, the activity of antibodies is also used as the basis of classification. For instance, IgG is the most common antibody present in blood and body fluids, while IgA is mainly found in the mucous membranes present in the respiratory and gastrointestinal tracts [19].

The production of native antibodies is usually related to the adaptive immune response, which is synthesized by plasma cells in the process of the humoral response. They destroy specific pathogens through several approaches, including agglutination, opsonization, and neutralization. In general, the production of native antibodies requires a relatively long time-about a few days or even a few weeks—so the innate immune response must take over to defend against the invasion of pathogens. However, this can cause serious conditions in the body, such as a cytokine storm, which can ultimately lead to systemic damage, multi-organ failure, or even death [21]. Therefore, treating the condition before the body produces antibodies as quickly as possible becomes fairly important.

3.1 Monoclonal antibodies

Monoclonal antibodies are immunoglobulins that have a high degree of specificity for a particular antigen or epitope. They are typically derived from a clonal expansion of antibody-producing malignant human plasma cells, so a type of monoclonal antibody can only target one type of epitope in a particular approach [22]. They can be produced in large amounts with the support of generic engineering in a relatively short time.

The initial monoclonal antibodies were created by fusing spleen cells from an immunized mouse with human or myeloma cells, forming the hybridomas that produced the desired antibody reactivity. However, these fused cells were problematic as therapeutic agents because they contained mouse proteins, which are rejected by the human immune system. Therefore, mouse-human monoclonal antibodies with a further "humanizing process" have been produced. Finally, the fully human recombinant monoclonal antibodies were developed [22].

At the beginning, monoclonal antibodies functioned as immunomodulatory agents with activity against specific immune cells, such as CD3 and CD4 cells, inhibiting some of the functions of these lymphocytes, especially after solid organ transplantation. Moreover, monoclonal antibodies were prepared to inhibit the function of cytokines. In addition, therapeutic monoclonal antibodies were developed for treating cancer or some serious viral infections [22]. Furthermore, the monoclonal antibody is a fairly important component of the antibody drug conjugate, which is responsible for carrying and targeting the abnormal cells or pathogens [22].

In conclusion, monoclonal antibodies show great potential in providing an alternative to current drug treatments, provided that in vitro cultivation and cloning techniques can be used efficiently and maturely.

3.2 Polyclonal antibodies

Different from monoclonal antibodies, polyclonal antibodies are produced during the polyclonal B cell response, producing a repertoire of antibodies that can recognize variant antigen epitopes [22, 23]. In the normal adaptive immune response, polyclonal antibodies are synthesized rather than monoclonal antibodies because the actual situation is much more complicated than monoclonal antibodies can effectively neutralize or destroy the pathogen. In general, polyclonal antibodies can be defined as a collection of monoclonal antibodies. The only difference is the synthesis process.

3.3 Antibody drug conjugate

The antibody-drug conjugate (ADC) is a humanized or human monoclonal antibody conjugated with cytotoxic small molecules via chemical linkers. The reason for choosing monoclonal antibodies is due to their high cell target specificity, long half-life in the human bloodstream, and minimal immunogenicity [24].

3.3.1 Action of ADCs

When the ADCs enter the bloodstream, the antibody component of the complex binds to the antigens on target cells or pathogens. The ADC-antigen complex enters the cell via endocytosis, packaging in the lysosomes. Then, the cytotoxic payload is released in an activated form, which interferes with DNA molecules or inhibits the function of RNA polymerase, leading to apoptosis [24].

Currently, ADCs are mainly used in the treatment of cancer, but if the cytotoxic payloads are altered into antimicrobial molecules, the destruction of bacteria will become possible.

3.3.2 Selection of chemical linker

Undoubtedly, the chemical linker needs to be a moiety that covalently tethers the antibody and payload components [24]. In addition, the linker needs to possess adequate stability in plasma, in order to circulate in the bloodstream and remain at the tumor site or invading site without premature breakdown. The connection also requires stability to prevent the unexpected liberation of the payload, which may cause damage to the healthy tissue or the harmless bacterial flora [24]. Moreover, the linkers need to possess the capacity to cleave rapidly and release the toxic payload once the ADC gets into the target cell

[24]. Furthermore, the linkers need to be hydrophobic to avoid the aggregation of ADC molecules [24].

4 Advantage of antibody drugs

Monoclonal antibodies are usually tolerated, which can stay in the blood plasma for a long time. Because they are relatively large polypeptides, they can last for a longer time in the blood compared to most antimicrobial molecules or antiviral drugs when the same dose is given. In addition, the metabolism of antibodies usually takes place in the liver, like other proteins, which are broken down into amino acids. These amino acids are used to synthesize other new proteins, and the excess ones are transferred into urea, which is released by the normal urinary process without any toxic metabolites production [22].

Moreover, the selection of antimicrobial agents requires a significant amount of time, and only one out of thousands of agents will obtain permission to enter clinical trials. In contrast, antibodies can be synthesized by cultivated immune cells with high specificity and low immune rejection, provided the antibodies are highly humanized. This can save time when resistant bacteria become an urgent issue or when a sudden outbreak is caused by unknown pathogens. Furthermore, monoclonal antibodies have high specificity, enabling them to target cancer cells or pathogens accurately while avoiding damage to normal cells and beneficial bacteria in the body. For example, the balance of gut flora may be easily disrupted by the intake of general antibiotics and requires a long time to recover.

Overall, the antibody drug has a longer half-life in the blood, harmless metabolic products, a faster development period, and lower damage to irrelevant cells.

5 Limitation of antibody-based drug and possible solution

5.1 Problems need to face

First of all, the convenience of taking the drug. Antibodies are a type of protein, so when they come into contact with the gastric acid in the stomach, the denaturation of the antibodies is fairly likely to occur. Therefore, the structure and function of the antibody may be damaged, which may prevent it from destroying the pathogen or delivering the cytotoxic agents to the correct places. Thus, direct oral administration seems impossible and may require encapsulation or direct injection. However, even when the antibody enters the bloodstream, it still may not reach certain parts of the body, such as the brain, due to the presence of the blood-brain barrier. Another method of administering the antibody is inhalation, especially in the treatment of serious lung diseases [25].

Nevertheless, the approach has some outstanding problems; the inadequate stability of antibodies is a prime obstacle, including denaturation and degradation in the lungs.

Immune rejection can still occur even with the humanizing process, so rejection reactions may happen. This is because non-human peptides may still be produced and recognized as non-self-antigens by the immune system.

The cost of cultivating in vitro immune cells is a frontier technology, so it is not mature enough, whereas the cultivation of antimicrobial-molecules-producing fungi or bacteria has had a relatively long period of time since the early last century.

5.2 Solutions

Artificial intelligence seems to show great potential in the biology field, especially in the development of antibody therapeutics [25]. Machine learning is likely to satisfy the demands of improving the affinity, potency, and developability of the antibody drug [25]. The learning machine can considerably save the time-consuming on the relevant process.

6 Conclusion

Antibodies are molecules produced by our body that have undergone continuous improvement over millions of years of evolution. These molecules offer significant advantages in defending against pathogen infections and in cooperating with the immune system. However, the natural production of antibodies faces various limitations, such as the time required for the immune system to synthesize adaptive antibodies, or issues related to the clones of plasma cells. Consequently, new technologies are required for more efficient methods of synthesizing antibodies or using antibodies as antibody-conjugated drugs to align with the use of drugs. This provides more options for the use of antibodies as immune molecules or as a new type of drug in modern therapy. It also reduces the pressure caused by drug resistance problems. Moreover, with the advancement of artificial intelligence, the process of producing antibody-based drugs can be modified for better approaches. Overall, antibody drugs show potential as an alternative way to manage drug resistance issues.

References

1. J. Tanwar, S. Das, Z. Fatima, S. Hameed, Multidrug resistance: an emerging crisis. Interdiscip. Perspect. Infect. Dis. 2014:541340 (2014)

ISSN 2959-409X

2. B. Spellberg, J. G. Bartlett, D. N. Gilbert, The future of antibiotics and resistance. N. Engl. J. Med. 368:299-302 (2013)
3. J. M. A. Blair, M. A. Webber, A. J. Baylay, D. O. Ogbolu, L. J. V. Piddock, Molecular mechanisms of antibiotic resistance. Nat. Rev. Microbiol. 13:42-51 (2015)
4. Z. X. Phuna, P. A. Kumar, E. Haroun, D. Dutta, and S. H. Lim, Antibody-drug conjugates: Principles and opportunities. Life Sci. 347:122676 (2024)
5. C. H. Song, M. Jeong, H. In, J. H. Kim, C.-W. Lin, and K. H. Han, Trends in the Development of Antibody-Drug Conjugates for Cancer Therapy. Antibodies. 12:72 (2023)
6. Z. Fu, S. Li, S. Han, C. Shi, and Y. Zhang, Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct. Target. Ther. 7:247 (2022)
7. R.F. Seipke, M. Kaltenpoth, and M. I. Hutchings, Streptomyces as symbionts: an emerging and widespread theme? FEMS Microbiol. Rev. 36:862-876 (2011)
8. J.L. Klassen, Microbial secondary metabolites and their impacts on insect symbioses. Curr. Opin. Insect Sci. 4:15-22 (2014)
9. M.F.Traxler, R. Kolter, Natural products in soil microbe interactions and evolution. Nat. Prod. Rep. 32:956-970 (2015)
10. P. Shree, C. K. Singh, K. K. Sodhi, J. N. Surya, and D. K. Singh, Biofilms: understanding the structure and contribution towards bacterial resistance in antibiotics. Med. Microecol. 16:100084 (2023)
11. A. Fàbrega, S. Madurga, E. Giralt, and J. Vila, Mechanism of action of and resistance to quinolones. Microb. Biotechnol. 2:40-61 (2009)
12. E.M. Halawa, M. Fadel, M.W. Al-Rabia, A. Behairy, N.A. Nouh, M. Abdo, R. Olga, L. Fericean, A.M. Atwa, M. El-Nablaway, and A. Abdeen, Antibiotic action and resistance: updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance. Front. Pharmacol. 14:1305294 (2024)
13. W.S. Champney, The other target for ribosomal antibiotics: inhibition of bacterial ribosomal subunit formation. Infect. Disord. Drug Targets. 6:377-390 (2008)
14. A. H. Delcour, Outer membrane permeability and antibiotic resistance. Biochim. Biophys. 1794:808-816 (2009)
15. Q. Vicens and E. Westhof, RNA as a drug target: the case of aminoglycosides. ChemBioChem 4:1018-1023 (2003)
16. J.M. Munita and C. A. Arias, Mechanisms of Antibiotic Resistance. Microbiol. Spectr. 4 (2016)
17. J.M. Manson, L.E. Hancock, and M.S. Gilmore, Mechanism of chromosomal transfer of Enterococcus faecalis pathogenicity island, capsule, antimicrobial resistance, and other traits. Proc. Natl. Acad. Sci. U.S.A. 107:12269-12274 (2010)
18. D.Ä.G.R.D. Ärzteblatt, The Diagnosis and Treatment of Tuberculosis. Deutsches Rzteblatt (2019).
19. The Editors of Encyclopaedia Britannica, Antibody | Definition, Structure, Function, & Types. Encyclopedia Britannica (2025).
20. S. Perdue, S. Scott, J. Humphrey, and H. J. (Encyclopedia Britannica), Immune system | Description, Function, & Facts. Encyclopedia Britannica (2025)
21. D. Jarczak and A. Nierhaus, Cytokine Storm-Definition, Causes, and Implications. Int. J. Mol. Sci. 23:11740 (2022)
22. National Institute of Diabetes and Digestive and Kidney Diseases, Monoclonal antibodies. LiverTox - NCBI Bookshelf (2025)
23. S.C. Oostindie, G.A. Lazar, J. Schuurman, and P.W.H.I. Parren, Avidity in antibody effector functions and biotherapeutic drug design. Nat. Rev. Drug Discov. 21:715-735 (2022)
24. K. Tsuchikama and Z. An, Antibody-drug conjugates: recent advances in conjugation and linker chemistries. Protein Cell. 9:33-46 (2016)
25. P. J. Carter and A. Rajpal, Designing antibodies as therapeutics. Cell. 190:1-21 (2022)