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Editorial overview

Editorial overview: Anti-viral strategies: Human antibody immune response and antibody-based therapy against viruses

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Qiao Wang is a Principle Investigator at the Shanghai Medical College of Fudan University. He studies the mechanisms of AID-dependent antibody diversification (somatic hypermutation and class-switched recombination) in B lymphocytes. Recently, he also investigates human B cell antibody immune response against different pathogens, including ZIKV, HBV and SARS-CoV-2, and explores novel therapeutic strategies for infectious diseases by using bNAbs.

Human antibody immune system evolves to fight foreign invaders and efficiently defends against diverse pathogens. Antibodies induced by vaccines also effectively protect against serious illness. Therefore, the use of monoclonal antibody (mAb) to prevent or treat virus-induced infectious diseases is a clear and well-reasoned clinical strategy. This year's Antiviral Strategies section of *Current Opinion in Virology* updates the research and development of mAbs against a number of important viruses, including human immunodeficiency virus (HIV) [1], Ebola virus (EBOV) [2], Hepatitis B virus (HBV) [3], influenza virus [4], coronavirus [5], human cytomegalovirus (HCMV) [6], and rabies virus [7]. Moreover, the development of a plant-based platform for producing mAbs against viral infections is also reviewed [8]. We hope the updated information in these review articles would greatly facilitate the future development of clinical antibody drugs against more traditional and emerging pathogens.

In 1998, a mAb against respiratory syncytial virus infection is approved by the U.S. Food and Drug Administration (FDA) as the first antibody drug to treat viral infection. Afterwards, mAbs against HIV and EBOV were both under preclinical or clinical evaluation [1,2]. Notably, during recent COVID-19 pandemic, mAbs against SARS-CoV-2, with emergency use authorization issued in many countries, have achieved great clinical success [5], further underscoring the significance and efficacy of using mAbs for prevention and treatment of viral infection.

Many methods have been adopted for screening and cloning of human mAbs, including combinatorial display library screening method, hybridoma technology using humanized mice, single-B-cell-based antibody cloning platform, and B cell-activation or immortalization method [9]. Among them, single-B-cell-based antibody cloning technology is most popular. Fluorescence-activated cell sorting (FACS)-sorted antigen-specific single B cell was originally used for nested-PCR amplification of anti-HIV broadly neutralizing antibodies (bNAbs) [1], while recently it is widely used for anti-SARS-CoV-2 antibody cloning [5]. The popularity of this method is due to its capacity to better reflect the real human antibody immune responses.

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The understanding of the human antibody response greatly facilitates the identification and selection of broadly and potently neutralizing mAbs. For example, the systematic and functional comparison of the mAbs between individuals with broad serum neutralizing activity and those without unraveled that anti-HIV bNAbs generally possess high levels of somatic hypermutation and long third heavy chain complementary-determining region sequences [1].

Characterization of human or mouse mAbs also improves the understanding of their recognized antigens and binding epitopes. Specifically, anti-HIV bNAbs target several distinct epitopes on the HIV envelope glycoprotein (GP), including its membrane-proximal external region, the gp120-gp41 interface region, the V1/V2 loop apex, the V3 loop base and surrounding glycans, and the CD4 binding site [1]. Anti-EBOV mAbs target various epitopes, including the receptor-binding domain (RBD), on the viral GP [2]. Human neutralizing antibodies against HBV antigen, HBsAg, mainly target its extracellular antigenic loop or major hydrophilic region, while could also target the PreS1 domain of L-HBsAg to block its binding with host receptor NTCP [3]. As for influenza, many broadly neutralizing antibodies against influenza A/B viruses recognize several binding epitopes on three major influenza virus surface proteins, HA, NA, and M2e [4]. Coronavirus spike (S) proteins are the major targets for mAbs, while antibodies against a variety of RBD epitopes are mostly neutralizing [5]. HCMV, with a very broad cell tropism, has multiple surface GPs targeting distinct host receptors, while mAbs against these viral GPs (gB, gM/gN complex, gH/gL/gO trimer, and gH/gL/pUL128/130/131 pentamer) are neutralizing [6]. Rabies G protein on the surface of the viral particles, with its ectodomain stabilized by several disulfide bonds, has six antigenic sites (I, IIa, IIb, III, IV, and 'a') and is the main target for antirabies neutralizing antibodies [7]. In conclusion, characterization of the Fab region of natural antibodies revealed various neutralizing epitopes on the viral surface proteins and facilitate the elucidation of the molecular mechanisms for neutralization.

Protein structural analysis is an efficient way to probe the antibody–antigen interaction. Many binding details have been revealed for anti-HIV, anti-influenza, anti-SARS-CoV-2, anti-HCMV, antirabies antibodies and so on, while structural studies about anti-HBV antibodies lags far behind due to the heterogeneity of the HBsAg antigen [3]. Structural analysis not only interrogates the epitope diversity of a panel of mAbs, but also reveals the structural details of highly conserved epitopes for bNAbs. The identification of these conserved epitopes has inspired and contributed to the design of broadly protective antiviral vaccines. For example, vaccination strategies, such as sequential immunization or delicate immunogen design, aiming at induction of bNAbs against influenza or HIV, are being investigated by several clinical trials [1,4].

Nevertheless, it is very challenging to identify bNAbs for many infectious viruses. Different genotypes, highly divergent subtypes and newly emerging variants containing various natural escape mutations could dramatically evade antibody recognition. Moreover, on the surface of antigens, glycans might affect the binding of antibodies by creating steric hindrance. Therefore, combination of bNAbs targeting two nonoverlapping epitopes is a common strategy to restrict viral escape and suppress viremia more effectively.

Fc part of mAb also plays an important role for viral elimination during infections. Antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and complement-dependent cytotoxicity are all mediated through Fc domain and could enhance antigenic uptake and presentation [10]. Although many evidences support that Fc-mediated effector functions are important as Fab-mediated *in vitro* neutralization, recent experimental results showed that mAbs lacking the Fc effector function and complement binding, when administered at a sufficiently high dose, also exhibit similar levels of *in vivo* prophylactic efficacy [11,12].

Furthermore, engineering the Fc part could enhance the binding affinity with FcRn, leading to significantly improved pharmacokinetics for clinically used mAbs. For example, M252Y/S254T/T256E (YTE) or M428L/N434S (LS) variants have more than 10-fold higher human FcRn binding affinity and more than threefold longer serum half-lives, thus are most commonly used in clinical trials for multiple antibodies.

With both Fab and Fc domains optimized, mAbs, nowadays, have been more and more used clinically. Passive immunization using bNAbs or complementary bNAb combinations could prevent viral infection (such as HIV, HBV, rabies and so on) with superior efficacy. Previously, polyclonal immunoglobulins obtained from hyperimmunized horses or immunized individuals were used, while human monoclonal bNAbs would have many obvious advantages: greater efficacy and breadth, improved safety with reduced side effects, longer *in vivo* half-life, lower cost of production, easier availability and higher consistency in product.

Significant antiviral activity of bNAbs also enables mAb-based therapeutic approaches for many infectious viruses [1–7]. Anti-HIV antibody treatment resulted in a prolonged viral suppression in a subset of patients. Anti-EBOV mAb-based treatment has shown superior efficacy. Human mAb against HBV dramatically reduced the circulating serum HBsAg level. Hospitalized patients with severe influenza benefited from the anti-influenza antibody treatment. During COVID-19 pandemic, antibodies targeting SARS-CoV-2 S protein alleviated symptoms and reduced the likelihood of serious illness in thousands of SARS-CoV-2-infected patients. Safe and potent anti-HCMV antibody would be urgently needed due to the lack of an effective HCMV vaccine. For rabies, antibody infusion into brain is extremely efficient in treating rabies-infected fatal mice.

Currently, clinical usage of bNAbs remains expensive, prompting the search for economical ways for antibody production and delivery. Plant-made mAbs that can be produced rapidly and economically have been tested in human clinical trials [8]. In addition, novel methods to express and/or administer mAbs are also under investigation, such as delivery of mAb-encoding nucleotide sequence into human body through DNA/RNA-based gene therapy or via adeno-associated virus.

Finally, at the end of this brief introduction, we sincerely thank all the authors' contributions, especially for those working under lockdown during the COVID-19 pandemic. These reviews for mAbs against viruses would be of great interest to many readers and would help us to better understand mAb, an increasingly used weapon in the battle against various viral infections.

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