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Review

Monoclonal antibodies for prophylactic and therapeutic use against viral infections

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ABSTRACT

Neutralizing antibodies play an essential part in antiviral immunity and are instrumental in preventing or modulating viral diseases. Polyclonal antibody preparations are increasingly being replaced by highly potent monoclonal antibodies (mAbs). Cocktails of mAbs and bispecific constructs can be used to simultaneously target multiple viral epitopes and to overcome issues of neutralization escape. Advances in antibody engineering have led to a large array of novel mAb formats, while deeper insight into the biology of several viruses and increasing knowledge of their neutralizing epitopes has extended the list of potential targets. In addition, progress in developing inexpensive production platforms will make antiviral mAbs more widely available and affordable.

Contents

1. Passive immunization with polyclonal sera

Passive immunization is based on the administration of serum from convalescent/vaccinated human donors or animals to attempt to prevent or control infection [1,2]. Whilst vaccines require time to induce immunity and depend on the host's ability to mount an immune response, passive immunization can provide immediate protection and is theoretically independent of the recipient's immune status. Following the development of anti-diphtheria serum by von Behring and Kitasato in the early 1890s [3], immune sera from convalescent humans were used to prevent or treat a range of viral diseases including measles, the 1918 pandemic flu, varicella-zoster virus, Bolivian hemorrhagic fever, Argentine hemorrhagic fever as well as Ebola and Lassa hemorrhagic fevers [4]. Moreover, some of the earliest attempts to cure veterinary diseases involved passive immunization with serum from recovered animals as was described in seminal attempts to 'cure' rinderpest in the 1890s [5]. Today, several pooled antiviral immunoglobulin products are still available on the US market including

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hyperimmune immunoglobulin preparations against rabies virus, cytomegalovirus, hepatitis B and C viruses, vaccinia virus, varicella-zoster virus, respiratory syncytial virus (RSV) and West Nile virus.

A common disadvantage of polyclonal preparations is that many of their constituent virus-specific antibodies are non-neutralizing [4]. Moreover, polyclonal sera have to be screened and treated due to risks related with the use of blood products. Problems associated with the use of polyclonal sera might also include batch-to-batch variation and difficulties in obtaining immune donors [1,6]. An alternative to polyclonal antibody preparations is offered through the development of monoclonal antibodies (mAbs).

2. Development of monoclonal antibodies

In 1975, Köhler and Milstein developed hybridomas at the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK [7]. Since then, technologies for generating and engineering mAbs have greatly improved and the industrialization of mAb production has resulted in a large number of antiviral mAbs being developed for preclinical and clinical studies. Fully human mAbs (Fig. 1A) with minimized immunogenicity can now be generated using methods such as phage display [8] and purified envelope glycoproteins in either monomeric or oligomeric forms and viral particles are two types of antigen that are commonly used as bait for panning antibody libraries [4]. These antibody libraries are either naïve for the viral antigen [9,10], or can be obtained from convalescent or immunized patients or animals.

The first antiviral mAb approved by the US Food and Drug Administration (FDA) was palivizumab (Synagis/MedImmune), a humanized IgG1 antibody that confers RSV prophylaxis in high risk infants [11,12]. Prior to palivizumab, prophylaxis of RSV disease depended on a polyclonal serum preparation called RespiGam (or RSV-IGIV). This polyclonal preparation showed relatively low specific activity, and dosing required the application of relatively large volumes of antibody in low weight infants [13,14]. The greater potency of palivizumab reduced the volume required to deliver a therapeutic dose to an infant and has improved RSV treatment by avoiding the side effects of pooled serum [13,14].

3. Antiviral immunity

Specific antibody titers have been identified as correlates of protection against various viral infections. Antibodies operate through various mechanisms, mediated by either their variable or constant regions. Highly selective binding to specific epitopes on the target antigen is a functionally crucial property that is mediated by the antibody variable domains [15]. The antibody constant domains include the Fc region and perform other important functions including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) [15]. ADCC and ADCP are mediated by Fcγ receptors while CDC is mediated by complement cascade proteins such as C1q and C5 [16]. Another function of the Fc region is extension of antibody half-life (21 days for human IgG) through interaction with the neonatal Fc receptor (FcRn) [17].

Antibodies can interfere with virus entry into a cell by various mechanisms [4]. One mechanism is inhibition of virus attachment to cell surface receptors. This can be achieved through antibody binding to viral spikes, thereby interfering with their ability to bind to cellular receptors [18]. The same effect is achieved by antibodies targeting receptors or co-receptors, thereby making the binding sites for viruses unavailable [19]. Another mechanism is post-binding/pre-fusion neutralization and interference with required conformational changes at the cell membrane or endosomal membrane by antibodies that target non-receptor binding regions [20]. Additional mechanisms of virus neutralization include antibody-mediated crosslinking of virions [21,22], resulting in their immobilization and agglutination, or inhibition of the release of progeny virus, observed e.g. for antibodies against influenza virus [23].

In general, virus neutralization is considered to occur when a sufficient number of epitopes on the viral surface are occupied by antibody. This 'occupancy' model, sometimes referred to as the 'multi-hit model', proposes that obtaining a sufficient antibody density on a virion is the most critical factor for neutralization, leading to inhibition of attachment to cellular receptors or interference with endosomal or plasma membrane fusion processes [24,25]. An alternative model of neutralization is the 'critical binding site' model which is compatible with both a single-or multi-hit theory of neutralization [4]. According to this model, neutralization depends on targeting essential binding sites and is less dependent on obtaining high antibody densities on the viral surface [4,26].

In addition to their ability to directly interfere with virus entry into a cell, antibodies can counteract viral infection by means of their Fc effector functions [27,28]. The extent to which effector functions contribute to protection appears to be specific for different viruses. For HIV-1, it has been demonstrated that a neutralizing mAb engineered not to activate complement is as protective as the wildtype antibody [29]. However, when both complement and the FcRn (neonatal Fc receptor) were abolished, the same antibody showed reduced *in vivo* protective capacity [29]. While these observations point to an important role of ADCC in HIV neutralization, Fc effector functions do not seem to be required for neutralization of several other viruses, e.g. the antibody Fc region and its associated effector functions are not necessary for neutralization of rabies virus [1]. Equine sera for rabies post-exposure-prophylaxis (PEP) in humans routinely consists of $F[ab']_2$ fragments which are prepared by pepsin digestion and are devoid of the Fc region [30].

In some cases, antibodies may also act as immunomodulators and certain antiviral mAbs have been shown to have a 'vaccine-like effect' [31,32]: mice infected with a murine retrovirus and subjected to a short immunotherapy with a neutralizing mAb of the IgG2a isotype remained healthy and mounted a long-lasting protective antiviral immunity with strong humoral and cellular immune responses. The endogenous antiviral antibodies generated in mAb-treated mice allowed containment of viral propagation and enhancement of memory cellular responses after disappearance of the injected mAb. The administration of the mAb permitted the development of a long-lasting endogenous antiviral immunity, pointing to an important role for infected-cell/antibody immune complexes for long-term protection mediated by short passive immunotherapy [31,32].

4. Viral escape mutants

For an effective immunoprophylaxis, the antigenic variability of circulating viral strains and the potential for emergence of viral escape mutants need to be considered. These considerations are of special importance in the case of influenza A viruses where both antigenic drift and antigenic shift occur naturally and in the case of HIV where formation of different quasispecies with many different virus variants drives immune evasion. RNA viruses possess RNA polymerases devoid of proofreading and repair capabilities which may result in the emergence of resistant mutants under selective pressure, such as mAb administration. Escape mutants can be generated *in vitro* under selective pressure of antibodies [33,34], as observed e.g. with mAbs against chikungunya virus. Intriguingly, high-throughput sequencing also detected the mutated residues associated with the chikungunya viral escapes in sequences derived from virus treated with a non-specific antibody although