CellPress

Review

Antiviral Monoclonal Antibodies: Can They Be More Than Simple Neutralizing Agents?

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Monoclonal antibodies (mAbs) are increasingly being considered as agents to fight severe viral diseases. So far, they have essentially been selected and used on the basis of their virus-neutralizing activity and/or cell-killing activity to blunt viral propagation via direct mechanisms. There is, however, accumulating evidence that they can also induce long-lasting protective antiviral immunity by recruiting the endogenous immune system of infected individuals during the period of immunotherapy. Exploiting this property may revolutionize antiviral mAb-based immunotherapies, with benefits for both patients and healthcare systems.

The Increasing Promise of Antiviral mAbs

Although mAbs currently constitute the main class of biotherapeutics, the possibility of using them to treat viral infections has received limited attention until recently. This contrasts with cancer and inflammatory diseases against which they are now widely utilized [1–3]. This is also paradoxical if one considers that the first commercial mAb was an anti-respiratory syncytial virus (RSV) antibody used to fight a pediatric respiratory illness. This situation, however, is reversing. Indeed, a flurry of human, or humanized, mAbs against H5N1 influenza virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV), hepatitis C virus (HCV), Ebola virus, Marburg virus, severe acute respiratory syndrome (SARS) virus, dengue virus, rabies virus, Hendra virus, Nipah virus, yellow fever virus, and West Nile virus have been described in the past few years [4–17]. Some of these mAbs are currently being tested in the clinic and include second-generation mAbs with improved neutralizing activity and/or novel target specificities [6,7,18–22]. This is especially true for HIV, which has dominated most of the reports dedicated to broadly neutralizing mAbs during the past 2 years. Finally, antiviral mAbs have already demonstrated partial efficacy when administered after HIV, HCV, or Ebola virus established infections [11,23,24], fueling the idea that they represent promising, high-added-value therapeutic agents.

Direct Mechanisms of Action of Antiviral mAbs

mAb therapy is a form of **passive immunotherapy** (see Glossary) that is classically intended to blunt viral infections via direct and rapid targeting of the infectious agent rather than via the triggering of a long-term immune response against it. This therapeutic approach contrasts with **vaccine** approaches that aim to stimulate the endogenous immune response of the host, in order to provide sustained protective immunity.

mAbs can diminish viral dissemination by direct action involving both their antigen-binding activity and the effector functions borne by their **Fc fragment**. So far, most antiviral mAbs with therapeutic potential have initially (and logically) been selected for their ability to neutralize virions via the recognition of viral surface antigens essential for receptor binding and/or entry into host

Trends

Antiviral monoclonal antibodies (mAbs) are promising, high-added-value biotherapeutics. During recent years, the number of antiviral mAbs developed against both acute and chronic viruses has grown exponentially, some of them being currently tested in clinical trials.

Antiviral mAbs can be used to blunt viral propagation through direct effects. They can also engage the host's immune system, leading to the induction of long-lasting protective vaccine-like effects.

The assessment of mechanisms at play in the induction of vaccine-like effects by antiviral mAbs will help in improving antiviral treatments.

Exploiting this effect will translate into therapeutic benefit for patients. The benefit will also help healthcare systems through the reduction of treatment costs.

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cells. Furthermore, direct recognition has also been shown to inhibit cell–cell transmission of virions in certain settings.

Most antiviral mAbs studied to date are immunoglobulin Gs (IgGs), that is, antibodies efficiently recognized by both the complement and the **Fcγ receptors (FcγRs)** borne by many cells of the immune system. In addition to complement-mediated inactivation of viral particles, and/or their phagocytosis, this also permits **complement-dependent cytotoxicity (CDC)**, **antibody-dependent cellular phagocytosis (ADCP)**, and **antibody-dependent cell-mediated cytotoxicity (ADCC)** to eliminate infected cells displaying viral antigens at their surface (Figure 1A). This, for instance, is the case of mAbs targeting the envelope glycoprotein (Env) of HIV (and other lenti-/retroviruses) that is exposed at the surface of virus-producing cells. Finally, Fc–FcγR interactions can also directly impact viral propagation via a mechanism called **antibody-dependent, cell-mediated virus inhibition (ADCVI)** (see [19,25–27] for more information on direct Fc-mediated antiviral effects). Thus, during immunotherapies, mAbs can impact viral propagation via a variety of direct mechanisms, possibly varying according to the virus, the viral antigen recognized and the antibody itself. However, there is now accumulating evidence that antiviral mAbs, upon interaction with different components of the immune system, can also operate via indirect mechanisms, that is, engagement of the host immune response, with effects lasting well beyond the treatment itself. Thus, similarly to vaccine approaches, mAb treatment could lead to the stimulation of the endogenous humoral and cellular immune responses in such a manner as to provide protective immunity ('vaccine-like effects').

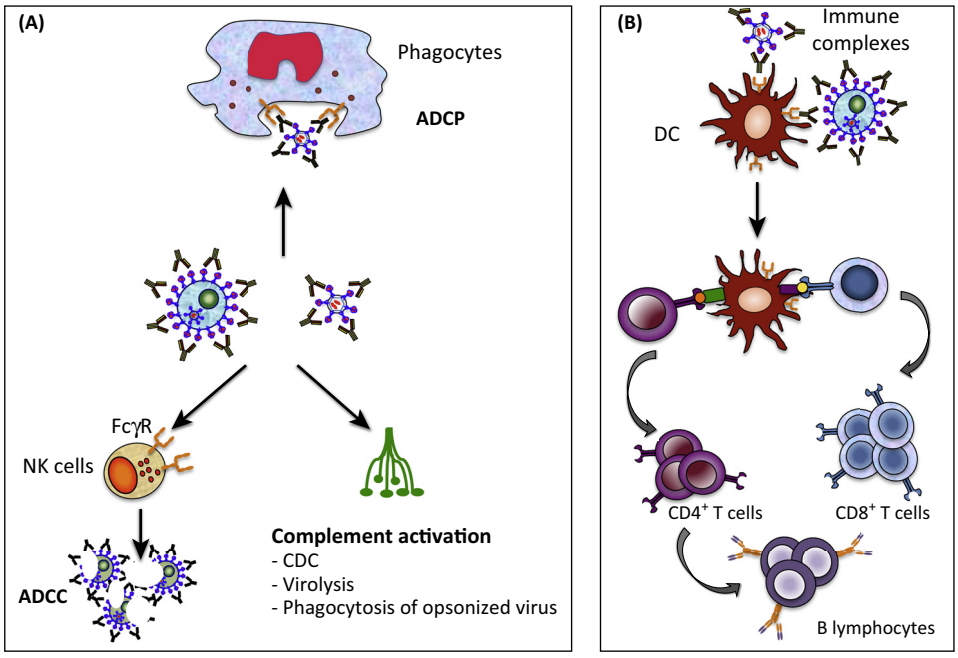

Figure 1. Fc Fragment(Fc)-Mediated Activities of Antiviral Monoclonal Antibodies (mAbs). (A) Upon administration, an antiviral mAb can opsononize virus, as well as infected cells if the viral antigen is also expressed on their surface. This can lead to virus elimination by complement activation and/or phagocytosis mediated by cells of the innate immune system. Infected cells can also be eliminated by complement-dependent cytotoxicity (CDC) as well as by antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody-dependent cellular phagocytosis (ADCP) mediated by FcγR-bearing effector cells. (B) Immune complexes (IC), constituted by mAb-coated virions or infected cells, can be recognized by FcγRs expressed on antigen-presenting cells such as dendritic cells (DC). Such IC recognition leads to enhanced antigen uptake and presentation, allowing induction of stronger humoral and cellular antiviral immune responses. Abbreviation: NK cells, natural killer cells.

Glossary

Antibody-dependent cell-mediated cytotoxicity (ADCC): a mechanism of cell-mediated immunity whereby effector cells of the immune system lyse a target cell that has been bound by specific antibodies. The Fc portions of the coating antibodies interact with Fc receptors that are expressed on immune effector cells (mainly natural killer cells or NKs), thereby initiating signalling cascades that result in the release of cytotoxic granules which induce the death of the antibody-coated cells.

Antibody-dependent cellular phagocytosis (ADCP): a mechanism of cell-mediated immunity whereby cells of the immune system phagocytose target cells that have been bound by specific antibodies. Similar to ADCC, the Fc portions of the coating antibodies interact with Fc receptors that are expressed on phagocytes (i.e., macrophages, granulocytes, and dendritic cells).

Antibody-dependent cell-mediated virus inhibition (ADCVI): a mechanism of antibody-mediated immunity wherey an infected target cell interacts with an effector cell expressing one or several FcγRs via a viral-specific antibody. ADCVI is a measure of the impact of antibody and FcγR-bearing effector cells on virus output from infected target cells and includes both lytic (i.e., ADCC) and non-lytic (i.e., production of chemokines) mechanisms leading to decreased viral spread.

Complement-dependent cytotoxicity (CDC): a mechanism of antibody-mediated immunity whereby antibody binding to the complement component C1q activates the classical complement cascade, leading to the formation of the membrane attack complex (the cytolytic end product of the complement cascade) and lysis of cells targeted by the antibody.

Fab fragment: the region of an antibody that binds to antigens. It is composed of one constant and one variable domain of each of the heavy and light chains (VH and VL, respectively).

F(ab')$_2$: two Fab fragments linked by a short fragment of the constant parts of the antibody (hinge region). It has the same affinity as the whole antibody and it is divalent.

Fc-engineered glycovariants: engineered antibodies in which the

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