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Review

Broadly neutralizing antibodies against HIV-1: Templates for a vaccine

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ABSTRACT

The need for an effective vaccine to prevent the global spread of human immunodeficiency virus type 1 (HIV-1) is well recognized. Passive immunization and challenge studies in non-human primates testify that broadly neutralizing antibodies (BrNAbs) can accomplish protection against infection. In recent years, the introduction of new techniques has facilitated the discovery of an unprecedented number of new human BrNAbs that target and delineate diverse conserved epitopes on the envelope glycoprotein spike (Env). The epitopes of these BrNAbs can serve as templates for immunogen design aimed to induce similar antibodies. Here we will review the characteristics of the different classes of BrNAbs and their target epitopes, as well as factors associated with their development and implications for vaccine design.

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Introduction

The global successes with many antiviral vaccines raise the question why the development of an HIV-1 vaccine is so challenging. Many of the difficulties lie in the distinct properties of this virus compared with other viruses. Foremost among these is the enormous sequence diversity of HIV-1, which can be as high as

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35% for the envelope glycoproteins (Env) between viruses from different subtypes (Gaschen et al., 2002; Hemelaar et al., 2006; Spira et al., 2003; Taylor et al., 2008). The relative inaccessibility of conserved domains on Env decreases the elicitation of protective antibodies with global coverage (Barouch, 2008; Walker and Burton, 2008). Moreover, the poor understanding of the immune responses that can control HIV-1 replication, for instance in elite controllers and high risk seronegative individuals, makes the development of vaccines that induce such immune responses rather difficult (Miura et al., 2009; Lederman et al., 2010).

It is assumed that a protective vaccine should elicit broadly neutralizing humoral immunity (Pantaleo and Koup, 2004; Walker and Burton, 2008), as passive transfer of broadly neutralizing antibodies (BrNAbs) can completely block infection by chimeric simian-human immodeficiency virus (SHIV) in non-human primate studies (Baba et al., 2000; Hessell et al., 2009a, 2009b; Mascola et al., 1999, 2000; Parren et al., 2001; Shibata et al., 1999). Furthermore, passive transfer of BrNAbs delays HIV-1 rebound after cessation of antiretroviral therapy in humans (Trkola et al., 2005). Recent studies in humanized mice and non-human primates have further delineated the potential of BrNAbs by showing vaccine-like protection against HIV-1 infection using gene-based antibody delivery (Balazs et al., 2012; Berkhout and Sanders, 2012). This review will focus on BrNAbs and how their characterization can guide the search for immunogens that elicit such BrNAbs and thus protect against infection.

Humoral immunity in HIV-1 infection

In order to better understand the immunogenicity of the HIV-1 Env and the host immune response against it, humoral immunity in the natural course of infection has been studied extensively. The majority of HIV-1-infected individuals mount an HIV-1-specific neutralizing humoral immune response within weeks to months after primary infection (Aasa-Chapman et al., 2004; Tomaras et al., 2008). This response is usually strain-specific as neutralizing activity is generally restricted to the autologous virus variants and mainly directed against the variable domains of Env (Gray et al., 2007; Li et al., 2006; Richman et al., 2003). The emergence of neutralizing antibodies (NAbs) is a burden to the virus and it drives the continuous evolution of HIV-1 Env. Longitudinal studies have shown that HIV-1 rapidly and repeatedly escapes from the NAb response mounted during HIV-1 infection (Bunnik et al., 2008; Deeks et al., 2006; Frost et al., 2005; Gray et al., 2007; Mahalanabis et al., 2009; Moore et al., 2009; Richman et al., 2003; Rong et al., 2009; Wei et al., 2003). As a consequence of this selection, the majority of the virus population in an infected individual is only weakly, if at all, neutralized by the contemporaneous antibody repertoire (Frost et al., 2005; Richman et al., 2003; Wei et al., 2003).

With time, as the virus population diversifies and the immune response matures, neutralization can also be detected against heterologous HIV-1 variants (Aasa-Chapman et al., 2004; Gray et al., 2007; Richman et al., 2003; Wei et al., 2003). During the first three years of infection approximately 20–30% of HIV-1 infected individuals develop broadly neutralizing activity with the ability to neutralize viruses from different subtypes (Binley et al., 2004, 2008; Simek et al., 2009; van Gils et al., 2009). In addition, about 1% of HIV-infected individuals, termed elite neutralizers, develop an HIV-1 specific neutralizing activity with remarkable potency and breadth (Euler et al., 2010; Simek et al., 2009). Unfortunately HIV-1-infected individuals do not benefit from broad or elite neutralizing antibody responses (Doria-Rose et al., 2009; Euler et al., 2010; van Gils et al., 2009). The lack of correlation between the presence of broadly neutralizing immunity and disease progression is explained in part by the rapid virus escape, but also by fading humoral responses during disease progression. The waning humoral immunity is exemplified by a decrease in autologous neutralizing antibody responses over time, probably as a result of the depletion of CD4+ T-cell help during chronic infection (Bunnik et al., 2008; Euler et al., 2010; Frost et al., 2005; Richman et al., 2003; Wei et al., 2003), as well as by the reduced responses of HIV-1 infected individuals to vaccination against other pathogens (Madhi et al., 2007; Veit et al., 2009).

Factors associated with the development of broadly neutralizing antibodies

To support HIV-1 vaccine development, more insight is needed into the host and viral factors that are associated with the ability of the host to elicit a BrNAb response, and how such a response evolves over time. The development of humoral responses in natural infection can provide clues as to what shapes a BrNAb response against HIV-1.

High antigenic load

Several studies have pointed out that the prevalence of broadly neutralizing activity in serum from elite controllers and viremic controllers is much lower as compared to typical progressors (Doria-Rose et al., 2009; Euler et al., 2010; Pereyra et al., 2008; Sather et al., 2009; Scheid et al., 2009). Together with a correlation between the development of broadly neutralizing activity and a high plasma viral RNA load, this suggests that the development of potently neutralizing humoral immunity apparently requires exposure to a sufficiently high amount of Env antigen.

High viral diversity

It has also been proposed that a higher degree of viral diversity increases the development of BrNAbs. Dual infection and co-infection can lead to more efficient induction of BrNAb, in particular when the superinfecting strain is from a different subtype (Cortez et al., 2012; Moore et al., 2011; Powell et al., 2010). In addition it has been shown that the viral diversity and divergence in individuals with broadly neutralizing activity is higher compared to individuals without broadly neutralizing activity, with the highest diversity being observed in an elite neutralizer (Euler et al., 2012; Piantadosi et al., 2009). Collectively these data suggest that viral diversity contributes to the formation of BrNAbs.

Prolonged antigenic stimulation

The development of a potent broadly neutralizing humoral immune response usually takes at least 2 to 3 years and the breadth of neutralization is correlated with the time since infection (Sather et al., 2009; van Gils et al., 2009), suggesting that prolonged antigenic stimulation may be required for sufficient antibody affinity maturation (McMichael et al., 2010; Stamatatos et al., 2009; Walker et al., 2010). Non-HIV-1 antibodies typically accumulate 5–15% changes in the heavy chain during affinity maturation, for example 3–12% in human anti influenza antibodies (Moody et al., 2011; Wrammert et al., 2011), however the known HIV-specific BrNAbs usually have a higher number of somatic mutations, ranging from 13% for b12 (Saphire et al., 2001), to 21% for PG16 (Walker et al., 2009), 32% for VRC01 (Wu et al., 2011), and 36% for NIH45–46 (Scheid et al., 2011) (Table 1). Furthermore, the heavy chain third complementary-determining