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Will studies in individuals with systemic lupus erythematosus be the key to future HIV vaccine design?

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Abstract

The induction of HIV-1 broadly neutralizing antibodies (bnAbs) remains the primary goal of a preventive HIV-1 vaccine but no HIV-1 vaccine candidate has succeeded in inducing bnAbs. All the bnAbs isolated from chronically HIV-1 infected subjects display one or more traits associated with control by host tolerance and immunoregulatory mechanisms, including reactivity against self antigens. Recent studies on a HIV-1 patient with concurrent systemic lupus erythematosus have informed on how similar bnAbs are to typical autoantibodies controlled by immune tolerance mechanisms. Future studies aimed at elucidating the intersection between autoantibodies generated in the context of systemic lupus erythematosus and the development of HIV-1 bnAbs will further our knowledge of specific roadblocks that hamper the production of bnAbs and, ultimately, inform us on how to implement vaccine strategies to circumvent them.

Keywords

autoreactive antibody; autoreactivity; HIV-1 broadly neutralizing antibodies; HIV-1 vaccine; HIV-1 vaccine design; immune tolerance; SLE; systemic lupus erythematosus

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As of 2013, more than 35 million people are living with HIV-1 and in 2012 alone an estimated 2.3 million people became newly infected [1]. After more than 30 years of the HIV-1 epidemic, there is still no cure and the development of a protective HIV-1 vaccine remains a global public health priority. Many licensed non-HIV-1 vaccines induce neutralizing antibodies that correlate with protection [2] and inducing sufficient and sustained titers of antibodies capable of neutralizing the multitude of circulating HIV-1 strains (called broadly neutralizing antibodies, or bnAbs) remains the primary goal of a preventive HIV-1 vaccine. However, despite decades of efforts, no vaccine candidate has yet succeeded in inducing HIV-1 bnAbs.

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Among chronically HIV-1-infected individuals, the breadth of serum HIV-1 neutralization spans a wide spectrum. While most people living with HIV-1 can generate serum responses with low-to-moderate breadth [3], only approximately 20% develop serum antibodies that neutralize a larger variety of HIV-1 strains and a mere 2–4% develop serum antibodies that broadly and potently neutralize a wide spectrum of diverse HIV-1 strains. Invariably, neutralization breadth requires 2–4 years to develop [4,5]. Antibody maturation is driven by increased affinity for autologous virus, whereas autologous virus mutants are selected based on their ability to escape autologous neutralizing antibody recognition (escape mutants) while maintaining adequate fitness [6]. The maturation of the virus-specific antibody repertoire and the autologous virus is intimately interconnected and is the result of both immune pressure and random mutations. Most of the heterosexually transmitted HIV-1 infections are initiated by the transmission of a single or few viruses ('transmitted/founder viruses') [7], and it can be argued that the infrequent generation of bnAbs during the course of natural infection may reside in the limited diversity generated from a single HIV-1-transmitted founder virus during the 'arm race' with the immune system compared to the formidable variability of circulating HIV-1 strains. However, despite its remarkable diversity, the HIV-1 envelope glycoprotein (Env) does present conserved regions that are accessible to bnAbs. We have previously demonstrated the presence of multiple bnAb specificities during chronic infection in a single individual, providing proof of concept that the induction of multiple specificities of bnAbs with a pan-neutralization profile is possible and a realistic goal for a preventive HIV-1 vaccine [8].

Up to 2009, only five bnAbs had been isolated, but now, with recent technical advances such as antigen-specific single-cell sorting, high-throughput PCR and clonal memory B-cell cultures, more than a hundred bnAbs have been identified that recognize multiple HIV-1 Env epitopes (reviewed in [9] and [10]). All bnAbs, regardless of their specificity, display one or more unusual traits associated with control, either direct or indirect, by host tolerance and immunoregulatory mechanisms – poly-and/or autoreactivity, long V-heavy complementarity-determining region 3 and unusually high levels of somatic mutations – indicating that naturally occurring bnAbs need to acquire atypical genetic changes through tortuous, non-linear maturation pathways [9,11]. It has been proposed that bnAb development may be limited and regulated by immune tolerance [12–14]. Perhaps the most compelling evidences supporting this mechanism of bnAb regulation come from studies of bnAb 2F5. BnAb 2F5 recognizes a highly conserved, well-exposed short linear epitope (ELDKWA) in the gp41 Env. By its inconspicuous nature, this epitope should be a very easy target for the immune system. However, 2F5-like bnAbs are exceedingly rare at best. Kelsoe and colleagues have elegantly demonstrated that bnAb 2F5 strongly and specifically binds to human kynureninase, a pyridoxal 5'-phosphate-dependent constitutive enzyme belonging to the class V group of aspartate aminotransferases, which presents the same ELDKWA epitope on its H4 domain and provided direct evidence that immunological tolerance can impair HIV-1 responses [15]. In a 2F5 VDJ knockin murine model, Verkoczy and colleagues have further demonstrated that B-cell development was almost completely blocked at the transition of small pre-B to immature B cells and that even when deletion mechanisms were circumvented, extant B cells displayed an anergic phenotype [16]. Haynes and colleagues demonstrated that bnAb 2F5 is a polyspecific autoantibody with anti-

cardiolipin reactivity and proposed that these kinds of antibodies may be produced by the same pool of B cells mobilized in autoimmune diseases such as systemic lupus erythematosus (SLE) and that their paucity is a reflection of obstacles in circumventing immune tolerance controls [13]. Since all known bnAbs carry signatures associated with negative selection through immunoregulatory control, the question as to why bnAbs are so rare should be, in reality, reverted: how do few people manage to make them despite their autoreactivity. A hypothesis is that the induction of bnAbs is a result of an at least partial breach of immune tolerance. Sanz and colleagues recently described that plasma neutralization breadth in HIV-1-infected subjects was partially mediated by an antibody idiotype (9G4-idiotype) that is characteristically expanded in SLE patients, supporting the notion that normal B-cell tolerance is impaired in at least a portion of HIV-1-infected subjects, albeit the degree to which B-cell tolerance is breached in persons with SLE may be different from persons with HIV-1 [17,18].

A corollary of this hypothesis is that HIV-1 subjects with immune tolerance dysfunctions should be more prone to make bnAbs and strong support for this hypothesis has now come from the recent finding by Bonsignori and colleagues of a bnAb (termed CH98) directed against the CD4-binding site (CD4bs) of the HIV-1 gp120 Env in an individual with both SLE and HIV-1 infection. BnAb CH98 was polyreactive and most notably, bound to dsDNA, a diagnostic criteria for SLE [19]. The molecular and phenotypic characteristics of bnAb CH98 were undistinguishable from other previously described CD4bs bnAbs isolated from chronically HIV-1-infected subjects, such as the similar CD4bs bnAb CH103 [6,19]. The evolution of the bnAb CH103 B-cell lineage has been recently characterized by Liao and colleagues, and, interestingly, the acquisition of neutralization breadth coincided with acquisition of reactivity against host antigens, including dsDNA [6]. Whether acquisition of overt auto- and polyreactivity and acquisition of neutralization breadth can be decoupled remains an open question.

Strikingly, the SLE/HIV-1 subject developed bnAb CH98 and plasma neutralization breadth while controlling viremia without receiving antiretroviral therapy. This is in stark contrast with what is observed in bnAb-producing non-SLE HIV-1 individuals and the general understanding that persistent antigen exposure is needed to drive bnAb maturation. These data suggest the intriguing hypothesis that antibodies generated in the particular setting of HIV-1/SLE may be able to control virus replication, albeit further studies are needed to confirm this notion. Interestingly, immunosuppressive therapy has been previously reported to be associated with increased HIV-1 replication and rapid progression of HIV-1 clinical course in a HIV-1/SLE subject, which is compatible with a role of SLE-induced antibodies in controlling HIV-1 replication [20].

It is possible that the immune dysregulations induced by SLE converted a disfavored and subdominant HIV-1 response into a more dominant antibody response, which is what an HIV-1 preventive vaccine should mimic, preferably without inducing autoimmune antibody reactivity. Further studies in HIV-1/SLE subjects should be conducted to describe the frequency of bnAbs in this population, the effect of the temporal relationship between HIV-1 infection and SLE onset on the HIV-1 antibody repertoire and the relationship between the HIV-1-specific and the autoreactive antibody repertoires: these studies will

likely inform on roadblocks that an effective HIV-1 vaccine should circumvent. Whether a vaccine immunogen can be designed to accomplish these goals is unknown. A vaccine design approach to achieve these goals is to use immunogens that optimally bind to selected ancestor and maturation intermediates of bnAbs and guide the development of B-cell lineages toward the desired mature bnAb ('B-cell lineage design') [6,12]. As a model for immunogen design geared to rescue subdominant responses, it is encouraging that in the 2F5 VDJ knockin mouse model, the anergic 2F5-expressing B cells that survived the B-cell developmental blockade were successfully rescued when mice were immunized with membrane-proximal external region–lipid complexes [16]. It should be noted that not all antibodies that react with host antigens are detrimental and it has been estimated that more than approximately 20% of IgG₊ memory B cells in the general healthy population have some degree of auto- and polyreactivity, including anti-dsDNA antibodies, without inducing clinical autoimmunity [21]. We believe that HIV-1 antibodies can be induced in a safe manner. Antigen-specific responses are commonly elicited in SLE subjects upon vaccination with well-characterized vaccines, such as the influenza and pneumococcal vaccines, even though at lower titers than the general population (recently reviewed in [22]) and comparing the immunogenicity of HIV-1 vaccine candidates – both at plasma and at single-cell levels – in people with and without SLE could provide valuable information to elucidate the direct contribution of dysregulations of tolerance mechanisms in shaping the immunogen-specific antibody repertoire in terms of antibody functions, maturation and B-cell populations targeted upon vaccination.

In conclusion, the recent studies on the HIV-1/SLE patient inform on how similar bnAbs are to typical autoantibodies that are controlled by immune tolerance mechanisms and have been critically instrumental in understanding the unusual biology of the remarkable host control of antibody responses against the well-conserved HIV-1 CD4bs bnAb epitope. Identifying more bnAb lineages in the rare HIV-1/SLE population, characterizing their maturation pathways, both molecularly and functionally, and comparing them with bnAb lineages isolated from non-SLE HIV-1 subjects will further our knowledge of the specific roadblocks that hamper the production of bnAbs and, ultimately, inform us on how to implement vaccine strategies to circumvent them.

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Biography

Mattia Bonsignori

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