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A Role for Antibodies in Natural HIV Control

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Abstract (198 words)

Purpose of the review

Rare patients naturally control HIV replication without antiretroviral therapy. Understanding the mechanisms implicated in natural HIV control will inform the development of immunotherapies against HIV. Elite controllers (EC) are known for developing efficient antiviral T cell responses, but recent findings suggest that antibody (Ab) responses also play a significant role in HIV control. We review the key studies that uncovered a potent memory B cell response and highly functional anti-HIV Ab in EC, and explore the mechanisms that may account for the distinct properties of their humoral response.

Recent findings

EC maintain a large HIV-specific memory B cell pool that is sustained by efficient Tfh function. Neutralizing Ab rarely show high titers in controllers, but seem capable, at least in certain cases, of neutralizing contemporaneous viral strains. In addition, EC display a unique HIV-specific Ab profile in terms of isotype, antigen specificity, and glycosylation pattern, resulting in polyfunctional Ab effector functions that may promote infected cell lysis and prime effectors of the antiviral immune response.

Summary

Lessons from EC studies argue for the importance of integrating the many parameters defining a polyfunctional Ab response when evaluating candidate vaccines and immunotherapeutic approaches directed at HIV.

Key words: HIV control, memory B cells, neutralizing antibodies, ADCC, CD4+ T cell help.

INTRODUCTION

Different groups of HIV-infected individuals naturally control HIV-1 (HIV) replication in the absence of combined antiretroviral therapy (cART): elite controllers (EC), who represent fewer than 1% of HIV-infected individuals and maintain very low to undetectable viremia (generally <50 copies HIV RNA/mL); viremic controllers (VC), who show partial viral control; and post-treatment controllers, who received cART but did not resume viral replication after treatment interruption [1,2]. Importantly, these groups of patients show a very low risk of progression to AIDS and usually maintain high CD4⁺ T cell counts [3]. In particular, EC show the strongest protection from disease and provide a unique opportunity to study immune responses involved in natural viral suppression [4].

It was long thought that cytotoxic CD8⁺ T cells (CTL) were the unique players involved in natural HIV control. Indeed, a fraction of EC exhibit potent CTL responses against HIV-infected cells, often associated with the expression of protective HLA alleles such as HLA-B*57 and B*27 [2]. However, a growing body of evidence suggests that the humoral response, sustained by efficient CD4⁺ T cell help, is also a key player in HIV control. In this review, we highlight the recent works that uncovered a potent memory B cell response in EC, and that demonstrated the capacity of EC's sera to perform multiple effector functions possibly involved in HIV control. We also examine the mechanisms that could underlie the development and persistence of HIV-specific memory B cells in EC, including the preservation of CD4⁺ T follicular helper (Tfh) cell functions and the possibility of more efficient antigen presentation.

Low Neutralizing antibody titers in EC

The role of the humoral response was initially neglected in the HIV control research field, as several studies had shown that EC had low HIV neutralizing antibody (NAb) titers as compared to viremic individuals [5-9]. In addition, EC with the lowest levels of HIV replication, who remained undetectable even in high-sensitivity viral loads assays (≤ 1 copy HIV RNA/mL), showed signs of low-intensity antibody responses, with fewer viral protein bands on HIV western blots, lower NAb titers, and lower cross-neutralization breadth [10]. Conversely, in viremic patients, the breadth of neutralization has been associated with higher viral loads [8,9,11-15], longer duration of viral exposure, and higher viral diversity [16]. In

other words, in EC as in viremic patients, the availability of viral antigens seems to determine the magnitude of the antibody response, as well as its cross-neutralization capacity.

It should be noted, however, that EC show a marked heterogeneity, with some presenting broad cross-neutralization capacity while others show minimal or no neutralization [5-8,17]. A flurry of broadly neutralizing antibodies (bNAbs) capable of neutralizing diverse HIV strains were identified during the past decade. Of note, some of the original bNAbs were cloned from HIV-specific memory B cells isolated from EC, indicating that these rare patients have the capacity to produce potent anti-HIV antibodies [17,18].

Preserved memory B cell differentiation in EC

Memory B cells, which are essential to sustain humoral immunity in the long-term, can be divided in 4 subpopulations: activated memory (AM), resting memory (RM), intermediate memory (IM) and tissue-like memory (TLM) B cells [19]. AM and TLM B cells, with the latter showing signs of anergy, are associated with higher levels of viremia [20,21]. In contrast, RM cells, which contribute to the long-term persistence of humoral responses, are decreased in progressor patients [19,22]. The picture that emerges is that of an abnormal immune activation that drives memory B cell exhaustion. cART decreases TLM and AM B cell proportions to near-normal levels in HIV-infected patients, but only restores the RM compartment in a subset of patients [20,23,24]. In EC, the proportions of the four memory B cell subsets are generally comparable to those observed in HIV-negative individuals [20,25]. However, the proportions of TLM B cells remain slightly elevated in EC, suggesting a degree of ongoing immune activation even in well-controlled HIV infection [20,25].

Potent HIV-specific memory B cell responses in EC

A key difference between EC and treated patients is that EC maintain a high frequency of HIV-specific memory B cells despite their low viral loads. These findings were obtained by measuring the frequency of circulating memory B cells capable of binding gp140 fluorescent probes [26] and by performing B cell ELISPOT assays [25]. Viremic patients who initiate cART show a marked decrease in the frequency of HIV-specific antibody-secreting cells (ASC), and patients treated in the long-term show low or undetectable HIV-specific ASC, consistent with the notion that viral replication is needed to constantly drive plasmablast differentiation in these patients [26-29]. In contrast, EC maintain a sizable memory B cell compartment despite limited antigenemia, suggesting that HIV-specific memory B cells are

either longer lived in these rare patients or still generated or renewed due to antigen/Tfh access in lymphoid structures even with very low blood antigenemia.

This is not to say that EC are free of HIV replication. EC are more and more often treated with cART, which decreases immune activation, slightly increases CD4⁺ T cell counts, decreases ASC frequency, and further decreases the viral load in these already well-controlled patients [26,30,31]. Simian models suggest that limited viral replication persists in the germinal centers (GC) of lymphoid organs in untreated controller monkeys [32]. It is thus conceivable that the persistence of HIV-specific memory B cells in EC depends on residual viral replication in GC, at the very site of antibody response maturation. Interestingly, residual HIV replication appears to drive a persisting low-grade inflammation in some EC and to influence B cell fates. A specific inflammation profile, characterized by increased levels of CXCL13, sCD40L, IP10, RANTES, and TNF α in plasma, has been associated with the capacity to develop cross-neutralizing antibody responses in EC [33]. Further studies confirmed the association between CXCL13 levels and the breadth of the neutralizing Ab response in EC, emphasizing the role of this chemokine in Ab maturation [34].

Association between memory B cells responses and HIV neutralization capacity

Several studies analyzed whether the persistence of HIV-specific ASC, which include plasmablasts and memory B cells, might correlate with the titers of HIV-specific Ab and/or the breadth of neutralization. Most studies carried out on heterogeneous cohorts of EC failed to observe a correlation between cellular B cell responses and the magnitude or neutralization capacity of the Ab response [13,28,35]. Interestingly, by dividing EC into two subgroups expressing or not the protective HLA-B*57 allele, we observed among HLA-B*57⁺ EC that the frequency of HIV-specific ASC correlated positively with the capacity to neutralize various HIV strains, including Transmitter/Founder viruses [25]. As EC show an early spontaneous control of HIV replication [36], which is probably mediated by CTL antiviral effect in HLA-B*57⁺ EC [37], we propose that these CTL responses might favor the establishment of efficient memory B cell responses with cross-neutralization capacity, through the rapid control of the viral load, which could in turn avoid B cell exhaustion and preserve Tfh function.

A role for autologous virus neutralization in HIV control?

HIV constantly evades the selective pressure imposed by NAb through mutational escape, so that at a given time the patient serum can neutralize previous but not contemporaneous viral strains isolated from the same patient [38]. Intriguingly, significant levels of autologous NAb (that is, capable of neutralizing the contemporaneous viral strains) were detected in viremic controllers [39]. Recently, an in-depth longitudinal characterization of the humoral response in a HLA-B*57+ viremic controller revealed that this patient harbored autologous NAb capable of neutralizing 88.5% of its circulating viral clones, suggesting that these NAb contributed to HIV control [40]. Interestingly, NAb in this patient could also cross-neutralize diverse heterologous HIV strains, suggesting that in some cases viral diversification can be efficiently matched by a diversification of the NAb response.

Preserved Tfh function may underlie the persistence of potent memory B cell responses in HIV controllers

Tfh cells, which reside within GC, provide help to B cells in the form of costimulatory signals and secretion of cytokines. Chronic HIV infection perturbs Tfh function, but paradoxically leads to an increase in Tfh numbers, which contributes to GC hyperplasia and lymphadenopathy [41]. Circulating Tfh (cTfh), defined as blood CXCR5+ CD4+ T cells, are thought to represent a form of memory Tfh, that can reacquire B cell helper functions upon antigenic stimulation [42,43]. Interestingly, an increased proportion of cTfh subsets that express PD-1 [44] or PD-1 in the absence of CXCR3 [45,46] was associated with the development of a broad HIV-neutralizing antibody response, in adults and children. This suggests that Tfh that experience ongoing antigenic stimulation, as measured by PD-1 expression, are needed to sustain continued antibody maturation in the context of chronic HIV infection.

HIV control is associated with the persistence of highly functional CD4 effectors endowed with polyfunctional cytokine secretion and cytotoxic capacities [47,48]. The expression of HIV-specific T cell receptors of particularly high affinity accounts for the persistence of CD4 effector responses in EC [49,50]. Recent studies indicate that Tfh function is also highly efficient in EC. The frequency of HIV-specific cTfh, as measured by MHC-II tetramer labeling, remains higher in EC than in treated patients, and correlates with a higher production of HIV-specific antibodies in memory B cells/cTfh cocultures [51]. In addition, HIV-specific Tfh defined functionally as CXCR5+ CD4+ T cells with IL-21 secretion capacity are also

preserved in EC, and show an association with the frequency of Env-specific memory B cells [52]. Thus, key Tfh/B cell interactions are preserved in controlled HIV infection, which enables continued antibody affinity maturation (see Graff-Dubois *et al.* in this issue). These findings emphasize the need to induce robust Tfh function in vaccination and immune restoration strategies targeting HIV.

A bias in Ab isotype and specificity in EC

In addition to pathogen neutralization, Abs accomplish a variety of effector functions, with Fc receptors (FcR) binding leading to cytokine secretion, antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC), and activation of the complement cascade. These different functions are strongly influenced by the immunoglobulin (Ig) isotype and the glycosylation status of the Ig Fc regions [53].

Although the IgG1 subclass dominates HIV-specific responses, the proportion of IgG isotypes varies depending on HLA type and clinical parameters [54-57]. A sequential study of Env-specific antibodies in controller and progressor patients showed that isotype profiles evolved over time, with a more prevalent Env-specific IgG2 response in controllers at early time points, while the IgG2 response developed more slowly in progressors [58]. In contrast, Env-specific IgG3 were present in both groups at early time points, but were progressively lost in progressors [58]. Isotype variations likely impact Fc-dependent functions, as for instance IgG1 and IgG3 generally bind Fc γ Rs with higher affinity than IgG2 and IgG4, with IgG3 being particularly efficient at mediating HIV internalization [59]. It is relevant that the loss of HIV-specific IgG3 occurs in synchrony with the loss of Fc-mediated functions that have been associated with viral control (see below) [60]. Accordingly, the sera from EC exhibiting strong polyfunctional antiviral activities are enriched in Abs of IgG1 and IgG3 subclasses [56]. Taken together, these studies suggest that the persistence of Env-specific IgG able to bind Fc γ Rs with high affinities could play a role in viral control.

Interestingly, HIV-specific IgA Abs were also detected at higher frequency in the sera of EC than in those of treated and viremic patients [61]. IgA responses in EC displayed broader antigen specificities and a particularly high avidity to the gp41 antigen [61]. Although serum IgA can clearly induce FcR-mediated phagocytosis of HIV [62], their phagocytic capacity appears reduced as compared to IgG1 and IgG3 [59]. However, IgA can engage Fc α RI to

trigger ADCC by monocytes and neutrophils, and IgG1 and IgA may actually cooperate rather than compete in the induction of FcR-mediated effector functions [63].

A role of Gag-specific antibodies in viral control has also been proposed. It is interesting that Gag-specific IgG2 [64,65] and IgG1 [66,67] have been associated with long-term nonprogression. Gag-specific IgG2 Abs seem particularly abundant in HLA-B*57-negative EC, and may reflect a role for the humoral response in viral control when the CD8 response is not dominant [57,68]. However, the significance of anti-Gag responses in HIV infection remains unclear, as Gag proteins are not expressed at the cell or virion surface, and should thus not be accessible to Abs. Gag-specific Abs may still be able to capture secreted Gag, broken virions, or infected cell fragments, which may in turn facilitate the uptake and presentation of Gag antigens to Gag-specific CD4⁺ and CD8⁺ T cells, which are immunodominant in EC and thought to play a key role in suppressing HIV replication [2,69].

A more potent ADCC function in EC?

HIV-specific ADCC, primarily mediated by NK cells, develops rapidly in the course of HIV infection and exerts an immune selective pressure on the virus, suggesting that it contributes to decrease the pool of infected cells during the early stages of infection [70-72]. Whether ADCC participates in viral control in EC during the chronic stage of infection remains debated [73]. Several studies did not detect an improved capacity of EC sera to mediate ADCC [56,74,75]. In contrast, Abs mediating ADCC were found to be increased in other EC cohorts [5,76], with one study reporting a predominant ADCC response in HLA-B*57-negative EC, as compared to HLA-B*57-positive EC [77].

These contrasting findings reflect the heterogeneity of ADCC responses in EC, but also the variable definitions of controller status in the different EC cohorts. The choice of the control group may also influence study outcome, as for instance viremic patients at an advanced stage of infection tend to show lower HIV-specific Ab levels in the circulation. There is clear evidence that the level of Env-specific Ab binding at the surface of infected cells is a correlate of ADCC activity [75]. Indeed, NAbs with an intrinsically higher capacity to bind the surface of infected CD4⁺ T cells show more efficient ADCC activity against these cells [78]. Competition between different types of antibodies may also influence ADCC function [79]. IgG3 are likely important in NK-mediated ADCC, as they have a particularly high affinity for FcγRIIIA, which is the only FcR expressed at the surface of NK cells in 80% of humans [80].

ADCC activity also depends on the strength of NK cell activation. Specific associations between certain NK cell receptors allotypes and their MHC-I molecule ligands, such as KIR3DL1 and HLA-B*57, influence disease progression and are associated with lower viremia [81]. Nonetheless, NK cells from EC and progressors have so far shown similar capacities to perform ADCC [56,74,82]. Therefore, the involvement of NK receptor allotypes in viral control may rely on the direct recognition of infected cells by NK cells, through NK receptor engagement rather than ADCC.

Polyfunctional Ab-effector functions in EC

Given the diversity of Ab effector functions, it seems unlikely that a single attribute of the Ab response may account for the unique capacity of EC to control HIV infection. To tackle this issue, Ackerman and Alter developed a systematic approach to study in a single sample an array of functions, including ADCC, NK activation, complement deposition (ADCD), ADCP, and Ab attributes, such as glycosylation status and FcR binding capacity [56,66]. This "systems serology" approach did not show a superior capacity of EC's sera to perform any of the above-mentioned functions. Rather, it revealed that the different Ab functions, except for ADCP, strongly correlated with one another in EC. In particular, ADCD correlated with all other functions, suggesting that EC developed a more coordinated Ab response than other patient groups [56]. EC exhibiting these polyfunctional antiviral activities had sera enriched in IgG1 and IgG3 HIV-specific Abs, pointing out to the importance of isotype subclasses in determining the overall quality of the antibody response [56].

Ab effector functions depend on binding to FcRs and to initiators of the complement cascade, with these steps being tightly regulated by the glycosylation of the Ig Fc region [83,84]. In humans, the IgG Fc-domain harbors a single glycosylation site that can accommodate up to 30 documented different glycan structures. In EC, a shift of the glycosylation profile toward agalactosylated glycoforms was observed in the total Ab pool [85]. In particular, HIV-specific Abs exhibited a high frequency of agalactosylated, afucosylated, and asialylated glycans [85]. These particular Ab glycoforms have been associated with enhanced FcR-mediated antiviral functions, and may thus account for the quality of Ab effector functions in EC. Interestingly, in EC, the presence of the particular glycoform G1S1F was strongly associated with emergence of HIV-specific IgG3, suggesting that coordinated changes underlie the development of polyfunctional Ab responses [66]. Overall, systems serology studies are

starting to shed light on the many interdependent parameters involved in defining the quality of antiviral Ab responses.

In addition to mediating direct antiviral activities, FcR-dependent Ab functions such as ADCP and complement deposition also enhance innate and adaptive immunity, by inducing cytokine secretion and promoting viral antigen presentation. For instance, injection of bNAbs in SHIV infected macaques and HIV-infected patients was shown to enhance T cell immunity and increase the neutralization breadth of endogenous Abs [86,87]. CD8⁺ T cell responses in particular were shown to contribute to durable viral control in bNAb-treated animals [88]. The underlying mechanisms are not elucidated yet, but may depend on increased formation of immune complexes and/or complement opsonisation (see Naranjo-Gomez & Pelegrin in this issue). Viral immune complexes were shown to promote antigen capture and dendritic cell (DC) maturation [89,90]. HIV immune complexes could also induce an antiviral state by triggering the production of type I interferon by plasmacytoid DC [91]. The enhancing effect of NAbs on adaptive antiviral immunity has yet to be fully investigated in EC, but it is interesting to note that DC from EC are more efficient at capturing HIV particles [92].

CONCLUSION

Increasing evidence suggest that humoral responses play an important role in natural HIV control. EC maintain a large HIV-specific memory B cell pool that is sustained by efficient Tfh function. NAb rarely show high titers in controllers, but seem capable, at least in certain cases, of neutralizing contemporaneous viral strains, and thus of directly contributing to viral control. In addition, EC display a unique HIV-specific Ab profile in terms of isotype and glycosylation pattern, resulting in polyfunctional Ab effector functions that may promote infected cell lysis and prime multiple effectors of the antiviral immune response. Lessons from EC studies argue for the importance of integrating the many parameters defining a polyfunctional Ab response when evaluating candidate vaccines and immunotherapeutic approaches directed at HIV.

KEY POINTS

- Persistence of a large HIV-specific memory B cell pool in EC
- Efficient Tfh help sustains memory B cells in EC
- Efficient neutralization of contemporaneous autologous viral strains in some EC and VC
- Increased frequency of Gag-specific antibodies in EC

- Persistence of Env-specific IgG3, which mediate NK-dependent ADCC in EC
- Shift of the HIV-specific IgG glycosylation profile in EC
- Polyfunctional Ab effector responses in EC
- Converging evidence that the humoral response plays a key role in natural HIV control

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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