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HIV-associated memory B cell perturbations

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Abstract

Memory B-cell depletion, hyperimmunoglobulinemia, and impaired vaccine responses are the hallmark of B cell perturbations inhuman immunodeficiency virus (HIV) disease. Although B cells are not the targets for HIV infection, there is evidence for B cell, especially memory B cell dysfunction in HIV disease mediated by other cells or HIV itself. This review will focus on HIV-associated phenotypic and functional alterations in memory B cells. Additionally, we will discuss the mechanism underlying these perturbations and the effect of anti-retroviral therapy (ART) on these perturbations.

Keywords

Memory B cells; HIV; anti-retroviral therapy; vaccination

Introduction

Human immunodeficiency virus (HIV) infects CD4+ T cells and induces CD4+ T-cell populations depletion, and progress to the acquired immunodeficiency syndrome [1]. In contrast to CD4+ T cells, HIV does not directly infect B cells, however, numerous B perturbations are discovered. For example, B cells are hyperactivated in HIV disease as shown in the elevated numbers of B cell spontaneously secreting immunoglobulin and exhibit hypergammaglobulinemia [2]. Simultaneously, B cells from HIV-infected patients also show impaired responsiveness to immunization *in vivo* and to B cell receptor-mediated

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signals *in vitro* [3, 4]. The plasma levels of antigen-specific antibody to both a T-cell–dependent antigen and a T-cell–independent antigen are decreased in HIV-infected individuals [5]. The reduced plasma levels of antigen-specific antibody are accompanied by reduced antigen-specific memory B cell responses [5]. Antibody levels and memory B cell responses offer different layers of humoral memory immunity to protect host from re-infection [6]. The impairment of serologic memory poses additional risks for HIV related opportunistic infection and mortality. Here, we will review the defects in humoral memory immunities associated with HIV infection focusing on memory B cell perturbations.

Memory B cell populations in HIV infection

Memory B cells are defined as cells that have encountered antigen and persist in the host after resolution of infection. These cells respond quickly and produce antigen-specific antibodies with improved affinity when challenge with the same antigen, and have the function of protection. A memory B cell is defined by having responded to antigen, as reflected by class switch and somatic mutation [6]. Historically, human memory B cells were distinguished by the IgD–phenotype [7], however a small population of IgD+ B cells with memory properties is also identified [8]. Currently, the tumor necrosis factor (TNF) receptor family member CD27 is widely accepted as a marker to define human memory B cell populations, comprising the IgM-IgD- class-switched memory B cells, IgM+IgD+ and IgM+IgD- class-unswitched memory B cells, and a very small population (less than 1% of peripheral B cells) of IgD+IgM- B cells [6]. Using the CD21 (complement receptor 2), which is down regulated in HIV-infected individuals [49] and is associated with B cell activation, classical CD27+ memory B cells could be further divided into activated memory B cells (AM, CD19+CD10−CD27+CD21−) and resting memory B cells (RM, CD19+CD10−CD27+CD21+) [9-14]. While CD27+ B cells constitute the majority of healthy human memory B cell pool, CD27−IgG+ memory B cells do exist in the peripheral blood, representing 1-4% of all peripheral B cells [15]. Accordingly, abnormal expanded CD27- memory B cells exist in HIV-infected individuals with the phenotype of CD19+CD10-CD27-CD21-, defined by tissue like memory B cells (TLM) [12, 13, 16].

HIV-associated loss of classical memory B cells

Activated and resting memory B cells

In 2001, De Milito A and colleagues reported that classical CD27+ memory B cells are depleted from peripheral blood in HIV-1-infected individuals [17]. This CD27+ memory B cell depletion can also occur in HIV-2-infected individuals [18]. After fractionating the CD27+ memory B cells into CD21+ cells (RM) and CD21− cells (AM), Moir S and colleagues found that while the frequencies of RM are reduced but AM are expanded in HIV-infected individuals [9]. The changes of reduced RM and increased AM are also detected in recent studies [19-21].

Memory B-cell subset alterations have also been investigated in different groups of HIV infection. Firstly, further depletion of RM occurs during chronic HIV infection when compared to RM from acutely HIV-infected patients [9]. Secondly, HIV elite controllers, a rare HIV-infected population with spontaneous viral suppression without CD4+ T cell

depletion and antiretroviral therapy [22], have an expansion of AM [19, 21]; however, it is not clear about the changes in RM in HIV elite controllers [19, 21]. Finally, memory B cells have also been assessed in HIV-infected individuals at the extremes of age. RM is relatively preserved in HIV-infected children under 1-year old and have depleted above 1-year old [23, 24]. With the depletion of RM, numbers of T cell-independent antigen (e.g., pneumococcal protein antigen)–specific memory B cells are reduced in HIV-infected children and adults [25, 26]. A recent study has analyzed the B cell subset alterations in young and aged HIV-infected patients and found that aging *per se* does not exacerbate the HIV-associated memory B cell alterations [27].

Class switched and class un-switched memory B cells

The classical CD27+ memory B cells can be defined as isotype class switched and un-switched subsets, while the switched memory B cells are memory B cells that have switched their immunoglobulin from IgM and IgD to other immunoglobulin classes IgG, IgA, or IgE [28]. Some studies report that circulating un-switched memory B cells, defined by surface expression of CD19+CD27+IgD+, are preferentially depleted in HIV-infected children and adults [25, 29], while the other studies claim that class switched memory B cells (CD20+CD27+IgD−) were depleted more profoundly in pediatric HIV infection [30], suggesting that immature immunity plays a role in B cell class switching. When IgM− is used to represent switched memory B cells, CD19+CD27+IgM−switched memory B cells are depleted in HIV infected individuals irrespective of antiretroviral status [31]. The depletion of CD19+CD27+IgM+ un-switched memory B cell is only seen in patients with CD4+T cell count less than 300 cells/μl [31]. Some studies used both IgM and IgD as the markers and show the percentage of CD19+CD27+IgM^{high}IgD^{low} un-switched memory B cells is significantly reduced in HIV infected individuals [26]. The median percentage of CD19+CD27+IgM−IgD−switched memory B cells in HIV-infected population is similar to that in health individuals, although twenty-five percent of HIV-1-infected individuals showed marked decrease of switched memory B cells [26]. B cell phenotypes are altered in HIV infection, making difficult to define markers of memory B cells for truly reflection of their function in HIV disease.

Mechanisms for the loss of classical memory B cells

Impaired generation of memory B cells

The mechanism of loss of classical circulating memory B cells from HIV-infected patients is not fully understood. Studies before the era of effective ART showed that antibody responses to vaccine antigens are impaired in HIV-infected immunocompromised individuals [32-34]. More recent studies usually included participants with higher CD4+ T cell counts. Long-term ART treatment still cannot fully restore vaccine Ab responses in HIV-infected patients [35, 36]. Nevertheless, patients with higher CD4+ T cell counts tend to have better antigen-specific antibody responses after vaccination [35-37]. Although the mechanism of maintenance serological memory and cellular memory may be different [38, 39], these two layers of humoral immunity tightly linked during B cell activation, differentiation, and antibody production. Therefore, impaired antibody responses to vaccination could result from memory B cell perturbation in HIV disease. Direct evidence of

impaired generation of memory B cells comes from studies showing that HIV-infected individuals tend to have reduced antigen-specific memory B cell responses against vaccination as compared with HIV-negative controls [4, 40]. Obviously, this impaired generation of memory B cells could be due to the lack of CD4+ T cell help, the inability of B cell response to CD4+ T cells may stem from reduced expression of CD25 on B cells during HIV infection [41, 42]. On the other hand, follicular helper T (Tfh) cells, which provide essential help to select and generate the high affinity antibody-producing B cells in B cell follicles [43, 44], are incapable of providing adequate help to B cells in the course of HIV infection [45]. This defect may be qualitative as there are increased frequencies of Tfh cells in lymph nodes of HIV-infected individuals, perhaps driven by persistent antigen stimulation [45-47]. Heightened programmed cell death-1 ligation may play a role in Tfh cell dysfunction [45]. In peripheral blood, there are also circulating CD4+ T cells that share functional properties with Tfh cells, namely peripheral Tfh [48]. These peripheral Tfh cells are depleted in HIV-infected individuals [49]. Anti-retroviral therapy could restore this depletion, but the peripheral Tfh cells are still functionally impaired which is associated with failure responses to influenza vaccine [50]. Taken together, the loss of memory B cells in HIV-infected individuals could stem from impaired T–B cell interaction.

Decreased survival of memory B cells

Another mechanism of the loss of classical memory B cells is the decreased survival of memory B cells in HIV disease [51]. Others and we have shown that memory B cells from HIV-infected individuals have impaired abilities to proliferate in response to TLR9 agonists CpG ODNs *in vitro* [51, 52]. Moreover, classical memory B cells are hyper-activated, characterized by highly spontaneous and activation-induced IgG secretion, and are prone to spontaneous apoptosis [17, 41, 53]. Fas (CD95) expression is up-regulated on memory B cells in HIV-infected patients, especially the HIV-viremic patients [17, 19, 20, 41, 54, 55]. Fas ligand may be up-regulated on memory B cells as well [17, 56]. The up-regulation of Fas on B cells could render them sensitive to Fas/FasL-mediated apoptosis *in vitro* [10, 55]. The Fas/FasL pathaway is involved in HIV-specific CD8 T cell apoptosis as well [57]. Microbial translocation, a driver for chronic immune activation in HIV disease, is correlated with the magnitude of immune restoration in treated HIV-infected patients [58, 59], implying its role in CD4+ T cell recovery after ART treatment. Of note, Fas expression on B cells in HIV-infected individuals is regulated by the concerted action of viremia, CD4+ T cell lymphopenia and T-cell activation [20]. Therefore, microbial translocation during HIV infection could be accompanied with high Fas expression on memory B cells. Indeed, we found such relation that Fas expression on memory B cells positively correlates with microbial translocation as reprinted by plasma lipopolysaccharide (LPS) levels in HIV-infected individuals [55]. HIV and LPS could synergistically induce memory B cells apoptosis *in vitro*. This effect is through Fas/FasL cell signaling pathway, with key involvement of plasmacytoid dendritic cells and type I interferon [55]. Additionally, Foxo3a and TRAIL signaling pathways also play a role in HIV-associated memory B cells apoptosis, which is related to the disruption of IL-2 signaling [60]. While TNF/TNFR pathway induces marked apoptosis of T cell in HIV-infected individuals [61], its role in B cell depletion in HIV disease is less clear. Finally, the increased memory B cell death in

HIV-infected individuals is associated with low levels of plasma nerve-growth factor (NGF) [53].

Increased differentiating into plasmablast/plasma cells

The dysfunction of B cell differentiation, including actively differentiating into plasmablast/plasma cells and impaired differentiation from naïve B cells to memory B cells, could be another mechanism for memory B cell depletion in HIV disease. HIV-infected individuals have elevated number of the terminally differentiated antibody-secreting cells in the periphery [9, 11]. Plasmacytosis has also been discovered in bone marrow in HIV disease [12]. Increased terminal differentiation of B cells in blood starts at early stage of HIV infection [62]. The majority of these cells are not HIV-specific, indicating non-specific and polyclone activation [63]. Many factors may contribute to the increased plasmablast/plasma cells in HIV-infected individuals. For example, *in vitro*, soluble CD27 binds to CD70 on B cells leading to activation of Blimp-1 and XBP-1, factors linking to B cells terminal differentiation and IgG production [64]. In the course of HIV infection, plasma levels of soluble CD27 are increased, correlated with disease progression [65] and serum levels of total IgG [64]. Moreover, T cells from HIV-infected individuals but not from healthy controls express CD70, the ligand for CD27, presumably could enhance the CD27/CD70 interaction, and lead to the memory B cells terminal differentiation [66]. Furthermore, elevated inflammatory cytokines such as IL-6 may also contribute to the increased terminal differentiation of B cells in HIV disease [67].

HIV-associated expansion of tissue like memory B cells (TLM)

In 2008, Moir S and colleagues described a unique memory B cell subpopulation, TLM with the phenotype of CD19+CD10−CD27−$CD21^{low}$, are expanded in HIV-infected patients [16]. The TLM are defined with the similar phenotypes of tonsillar tissue memory B cells with high-level expression of inhibitory receptors such as Fc-receptor-like-4 (FCRL4) [68]. TLM are considered exhausted B cells as they respond poorly to B cell stimuli and have expression patterns of inhibitory receptors and homing receptors,$CXCR3^{high}CD11c^{high}CCR7^{low}$CD62−, similar to those described for antigen-specific T cell exhaustion [69-71]. Moreover, expansion of TLM is associated with impaired immune surveillance [72]. Interestingly, HIV-specific B cells are enriched in these exhausted tissue-like memory B cells[16], and HIV specific responses could be enhanced by siRNA down regulation of inhibitory receptors such as FCRL4 and sialic acid-binding Ig-like lectin 6 (Siglec-6) [73]. While TLM are consistently found to be accumulated in HIV viremic patients [9, 16, 19-21, 72], whether this B cell subset is increased in HIV elite controllers is not clear [19, 21]. Aside from HIV infection, similar B cell subsets are expanded in many diseases with chronic inflammation, such as chronic HCV infection [74-76], chronic infection of plasmodium falciparum[77, 78], rheumatoid arthritis [79], and systemic lupus erythematosus [80].

Although TLM are expanded under heightened chronic antigen stimulations in HIV disease, whether it represents a protective response or an immune evasive strategy against pathogens remains largely unknown. Moreover, HIV-specific responses are enriched in exhausted TLM by detecting the HIV gp120-specific B cell frequencies by enzyme-linked immunospot

(ELISPOT) assay following polyclonal stimulation to induce terminal differentiation of all memory B cells [16, 69]. However, the different abilities of survival and proliferation in B cells in response to polyclone stimulation *in vitro* may generate bias to interpret the data *in vivo*. In a recent study, Kardava, L and colleagues re-evaluated HIV-specific responses in different memory B cell subsets using HIV envelope gp140 probes [81]. The AM, RM and TLM contribute to 50.9%, 31.2% and 16.1% of total HIV-specific responses, respectively [81], suggesting that the majority of HIV-specific responses are within CD27+ classical memory B cells population (50.9% plus 31.2%). The question raised from these studies is that TLM have a higher frequency of HIV-specific responses by ELISPOT [16] but a lower frequency of HIV gp140-specific B cells in TLM by flow cytometry [81]. One explanation is that memory B cells of the HIV-infected individuals tend to undergo apoptosis or deficiencies in proliferation [41, 53] therefore they may be undercounted by ELISPOT *in vitro*, but HIV envelope probes do not need *in vitro* stimulation. Of note, HIV envelope can non-specifically bind to B cells with non-BCR (B cell receptor), such as CD21 through complements [82, 83], mannose C-type lectin receptors [84], and integrin α4β7 [85]. This limitation of non-specific binding of HIV envelope to memory B cells should be overcome and be taken into consideration during interpretation the results. Nevertheless, classical memory B cells dominate HIV-specific responses in infected individuals [9, 21, 81].

Mechanism for HIV-associated expansion of TLM

TLM are expended when foreign antigens or self antigens persistently exit, this may be a consequence of chronic immune activation and/or inflammation [69]. Although expressing inhibitory receptors, the antigen-specific responses are still maintained in this exhausted cell subset [16, 73, 76]. Moreover, reduced levels of the antigens are associated with reduced frequencies of TLM [9, 21, 76, 78]. Therefore, it is possible that the expansion of TLM is driven by the chronic antigen stimulation. Microbial translocation would further increase the antigen burden in untreated HIV-infected patients [86], and may exacerbate the expansion of TLM. The exact mechanism underlying how persistent antigenemia induces expansion of TLM is unknown. Furthermore, plasmacytosisis is one of the remarkable characters of HIV infection [9, 63, 66]. CD27 is involved in the terminal differentiation to plasma cells [87], whether down regulation of CD27 on memory B cells is a strategy of immune system to alleviate the plasmacytosis is unclear. Of note, plasma levels of soluble CD27 are elevated in HIV-infected individuals and correlate with disease progression [65]. It would be of interesting to known whether this elevated soluble CD27 is, to some extent, due to proteolytic cleavage of CD27 on antigen experienced memory B cells. If this mechanism does exist, it would further contribute to the loss of CD27+ classical memory B cells. One of the characters of TLM is the high expression of FCRL4, an inhibitory receptor [16]. The dysfunction of TLM may in part stem from the high expression of FCRL4 because down-regulation of FCRL4 leads to improved B cell function [73]. Recently, Jelicic, K and colleagues showed that, *in vitro*, HIV envelope protein gp120 could bind to integrin α4β7 on human primary B cells and induce FCRL4 expression through TGF-β1 signaling pathway, resulting in impaired B cell proliferation [85]. Of note, plasma TGF-β1 level is increased in HIV-1-infected individuals [88], whether this pathway is involved in the expansion of TLM during nature HIV infection needs further studies.

Effect of ART on memory B cell perturbations

Phenotypic changes of memory B cell after anti-retroviral therapy

There is no evidence for the improvement of ART on classical memory B cell depletion in previous studies [17, 54]. Moreover, recent studies have demonstrated a effect of ART on memory B cell perturbation [9, 20, 21, 23, 27, 70, 89, 90]. After one year of ART, there is an increase of RM and decrease of AM and TLM [9]. ART at the early stage of HIV infection better preserves RM and leads to improved memory B cell responses to seasonal influenza vaccine [9]. Perturbation of AM and TLM, but not RM, seems to be further improved by prolonged ART [27]. Consequently, control of viral load and the recovery of CD4+ T cells lead to normalization of AM and TLM subpopulations but not RM [20, 21]. Study from another research group has found similar effect of ART on AM and TLM [89], but RM subset is normalized in younger patients [89]. Likewise, if HIV-infected children start ART at the age of 2 to 5 years old, age-dependent loss of RM can be restored [23]. Taken together, ART helps to correct abnormal expansion of AM and TLM and a less extent depleted RM. Early initiation of ART is useful to the recovery of B cell perturbation.

During HIV infection, classical memory B cells increase the expression of Fas, CD38 and CD70 and down regulate the expression of LAIR1 and CD25 [17, 20, 27, 41, 54]. Early studies showed that ART decreases Fas and CD38 expression on memory B cells but expression of Fas does not return to the normal level [41, 54]. Recent study found a complicated regulation of Fas by concert effect of HIV viremia, lymphopenia and T-cell activation [20]; and ART did not normalize heightened level of Fas expression on RM [20]. On contrast, expression of CD70, CD25 and LAIR1 on memory B cells are usually unaffected by ART [20, 27, 41]. However, initiation of ART during primary HIV infection may help to improve the expression of CD25 and LAIR1 on memory B cells [41]. Collectively, several markers that abnormally expressed on memory B cells may not be completely corrected by ART. This perhaps may lead to incomplete restoration of RM.

Effect of antiretroviral therapy on the antigen-specific memory B-cell pool

In accordance with the depletion of classical memory B cells, serum levels of antigen-specific antibody (HIV-unrelated antigens) titers as well as antigen-specific memory B cell frequencies are reduced in HIV disease [5, 91]. Moreover, defects in B cell memory subsets are associated with impaired vaccination responses, as indicated by reduced post-vaccination antibody levels [26, 92]. There is evidence that ART alone does not lead to an increase of plasmameasles-specific antibody levels after previous immunization in a longitudinal study [5]. For this reason, re-vaccination may be needed to reconstitute serologic memory. Most of the studies use levels of antigen-specific antibodies as an index to evaluate vaccine efficacies. Among these studies, ART has been found to improve humoral immune responses to vaccination in HIV-infected individuals, especially in patients with viral suppression and higher CD4+ T cell counts [93-95]. Nevertheless, frequencies of antigen-specific memory B cells against measles vaccine are not increased in children after 5 years of ART [90], suggesting that ART alone may be incapable of restoring the depletion of antigen-specific memory B cell pools. Failure of CD4+T cell recovery after ART in HIV-infected individuals has reduced frequencies of memory B cell responses against influenza

vaccine [40]. Starting ART early may improve memory B cell responses against vaccine due to the profound CD4+T cell recovery [96]. Indeed, better antigen-specific memory B cell responses against vaccine have been demonstrated in several studies in early ART treatment [9, 24, 90]. Moreover, children who started ART within the first year of life even have comparable antigen-specific memory B cell responses against measles vaccine [24]. Intriguingly, recent study has shown that antigen-specific memory B cell responses in repeat vaccinated HIV-1 infected patients on ART are not impaired [97]. Taken together, ART should be starting early in order to maximally preserve memory B cell function. For those HIV-infected patients who already have experienced a loss of antigen-specific memory B cells, re-vaccination may be a choice to reconstitute antigen-specific memory B cell pools.

Conclusion

HIV infection induces phenotypic and functional perturbations of memory B cells. ART partially restore B cell perturbation but recovery of RM B cell pools seems difficult unless earlier ART treatment. ART is unable to restore impaired humoral responses in HIV-infected individuals, and re-vaccination may be necessary. Optimizing vaccine strategy could help to enhance memory B cell responses against vaccine. Although numerous studies have demonstrated accumulation of CD27−CD21− memory B cells during HIV infection, the exact role of this cell subpopulation in HIV immunopathogenesis is not fully understood. To maximally limiting HIV-associated memory B cell perturbations, early initiation of ART should be taken into consideration.

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