Immune responses during spontaneous control of HIV and AIDS: what is the hope for a cure?

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HIV research has made rapid progress and led to remarkable achievements in recent decades, the most important of which are combination antiretroviral therapies (cART). However, in the absence of a vaccine, the pandemic continues, and additional strategies are needed. The ‘towards an HIV cure’ initiative aims to eradicate HIV or at least bring about a lasting remission of infection during which the host can control viral replication in the absence of cART. Cases of spontaneous and treatment-induced control of infection offer substantial hope. Here, we describe the scientific knowledge that is lacking, and the priorities that have been established for research into a cure. We discuss in detail the immunological lessons that can be learned by studying natural human and animal models of protection and spontaneous control of viraemia or of disease progression. In particular, we describe the insights we have gained into the immune mechanisms of virus control, the impact of early virus–host interactions and why chronic inflammation, a hallmark of HIV infection, is an obstacle to a cure. Finally, we enumerate current interventions aimed towards improving the host immune response.

1. Introduction

Since the first human immunodeficiency virus (HIV) was isolated 30 years ago [1], remarkable progress has been made in research and drug development, but an efficient vaccine against HIV/AIDS is still not available. Multiple obstacles must be overcome, including the fact that HIV has a remarkable capacity to accumulate mutations and escape adaptive immune responses. During the viral life cycle, the genetic material of the virus is integrated into the cellular genome, which is believed to allow the virus to evade the host’s immune responses. In this way, HIV can persist for months and years. Furthermore, HIV infection is characterized by the induction of immunological dysfunction, and consequently the host fails to control viral replication. Moreover, the preferential target cells of HIV are activated CD4+ T cells. Indeed, large quantities of virus particles are produced in activated CD4+ T cells, whereas resting CD4+ T cells are weakly or not permissive for HIV, and other CD4+ cells, such as macrophages, produce only small numbers of virions. HIV infection is characterized by a significant and persistent increase in activated CD4+ T cells. In other words, HIV creates and multiplies in its own target cells. Many open questions remain unanswered. For example, it remains a matter of debate whether a vaccine against AIDS should induce anti-HIV T cells or anti-HIV antibodies or both, which qualities anti-HIV T cells should possess and how and where antibodies must be produced. In the absence of a vaccine, alternative strategies have become more important. Recent progress in HIV research has raised hopes for a cure for HIV. The ‘towards an HIV cure’ initiative launched by the International AIDS Society has established a number of priorities with the aim of HIV eradication or at least lasting remission of infection during which the host can control viral replication in the absence of antiretroviral drugs (figure 1) [2]. Timothy Brown, an HIV-infected patient who received a double stem cell transplant from CCR5Δ32 donors [3], has...
lived for more than 6 years without the signs of the virus and represents the closest example to an HIV cure to date [4,5]. However, achieving HIV eradication in a large population of patients seems farfetched at present. The natural models of AIDS control and the cases of patients able to control replication after treatment interruption encourage us to believe that HIV remission may be an achievable goal.

2. Spontaneous protection against HIV/AIDS

The capacity to control HIV replication and the speed of progression towards AIDS vary among patients. Approximately 10% of individuals infected with HIV-1 maintain their CD4+ T cell counts at near-normal levels for more than 7 years in the absence of antiretroviral treatment. These individuals are called long-term non-progressors (LTNPs). Although LTNPs are a heterogeneous population, most LTNPs exhibit low levels of viraemia. Two extreme profiles within the LTNP population have been reported (table 1). On the one hand, a very few LTNPs maintain their CD4+ T cells despite high levels of viraemia (at least 10,000 copies of viral RNA ml⁻¹ of plasma). These individuals are called viroemic non-progressors (VNP). Because viral replication is not controlled in VNP, these individuals must possess a mechanism that protects them against CD4+ T cell loss and HIV-induced immunodeficiency. On the other hand, less than 0.5% of individuals infected with HIV-1 exhibit a spontaneous, highly efficient control of viral replication. This control is so effective that the viral load is often undetectable in the blood by routine clinical assays. Patients exhibiting such control for long periods are termed ‘elite controllers’ or ‘HIV controllers (HIC)’ [6]. The HLA alleles B27 and B57 are highly enriched in this population. However, the presence of these protective HLA alleles is neither sufficient nor always necessary to achieve control of infection.

3. Early virus – host interactions and their impact on disease progression

The risk of progressing rapidly or slowly towards AIDS can be somewhat predicted shortly after infection. Viraemia levels at six months post-infection predict the rate of disease progression [7]. The levels of T cell activation as measured by the frequency of CD8+ T cells expressing HLA-DR and CD38 also predict the disease progression profile [8]. Notably, T cell activation is a stronger predictor than virus viraemia [8,9] and is predictive even before seroconversion [10]. Recent studies demonstrate that inflammatory and coagulation biomarkers, such as IL-6, sCD14 and D-dimer, are better correlated with mortality than is T cell activation [11,12]. Moreover, the levels of certain inflammatory molecules during acute infection, such as IP-10, are better predictors of rapid disease progression than viraemia or CD4+ T cell counts [13].

Early virological and immunological features may be strongly prognostic because they reflect the presence of protective host factors (such as HLA-B27) and/or because the balance that is established between the virus and the host during the early phase of infection impacts the subsequent evolution of the infection [14,15] (figure 2). Therefore, beginning combination antiretroviral therapy (cART) during primary infection may provide significant benefits to HIV-infected patients. It has been suggested that early treatment could have a favourable impact on the reduction of viral reservoirs, the preservation of immune responses and protection from chronic immune activation [16]. It was recently reported that some HIV-infected patients who interrupted prolonged cART that was initiated shortly after primary infection can control viraemia [17]. Such post-treatment controllers (PTCs) have achieved control of infection through mechanisms that are, at least in part, different from those commonly observed in HICs. Indeed, PTCs had more severe primary infections than did HICs (figure 2). Importantly, most PTCs lacked the
Table 1. Extreme profiles of natural protection against HIV/AIDS. ADCC, antibody-dependent cell-mediated cytotoxicity; cART, combination antiretroviral therapy; TCM, central memory CD4<sup>+</sup> T cells; TFH, CD4<sup>+</sup> follicular T helper cells.

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protective HLA B alleles (B*27 and B*57) and instead carried risk-associated HLA alleles (i.e. HLA*B35) that were largely absent among the HICs. Accordingly, PTCs had poorer CD8+ T cell responses than did HICs. PTCs also had lower levels of T cell activation than HICs. Therefore, the mechanism of virus control seems different between PTCs and HICs.

It is likely that infection control in PTCs was not achieved spontaneously but was favoured by the early initiation of therapy. The frequency of PTCs is estimated at between 5% and 15% of patients beginning cART shortly after primary HIV infection [17–20], which is significantly higher than the proportion of HICs [21,22]. Such a significant proportion of PTCs has been observed only after early initiation of treatment and not when therapies were begun during the chronic phase, in which reported cases are even scarcer [23]. The rarity of PTCs worldwide may be explained by the fact that only a very small proportion (approx. 2%) of patients in the French Hospital Database on HIV who were identified during primary infection initiated early cART and experienced a treatment interruption [17]. Indeed, in the absence of a reliable marker to predict the outcome, therapy discontinuation, even if started early, is not recommended outside clinical structured protocols. Non-controlled infection after treatment interruption increases risks of morbidity and mortality [24] and also of infection transmission.

PTCs were able to control viral replication in the long term and, in some cases, even exhibited a progressive decrease in viral reservoir [17]. This may be at least partially related to the weak contribution of long-lived cells, such as central memory CD4+ T cells (TCM), to the total circulating reservoir in these individuals. It will be of interest to understand why PTCs can control viral replication. The fact that it may be feasible to help the host develop protective responses gives substantial hope for the development of a cure. However, most patients are diagnosed with HIV only after several years of infection and in addition the ability to translate the PTC’s mechanisms of control to other patients is as yet uncertain.

4. Animal models of spontaneous protection

Animal models allow a deeper understanding of early virus–host interactions, particularly with respect to the compartments that are crucial for the education of adaptive immune responses or that represent the major sites of viral replication (lymph nodes and mucosa). The only animal model that fully reproduces the physiopathology of AIDS consists of Asian monkeys (macaques) infected with simian immunodeficiency virus (SIV)mac. In recent years, the macaque/SIVmac model has revealed key characteristics of HIV-1 pathogenesis. For example, this model has demonstrated the impact of the viral protein Nef in maintaining a high viral load in vivo and for disease progression [25,26]. This model has also highlighted the role of CD4+ TCM as main targets of the virus in vivo [27–29], as well as the dramatic and rapid depletion of CD4+ T cells in the gut [30], and has contributed to demonstrating that microbial translocation is associated with disease progression [31]. Finally, the macaque/SIVmac model has revealed the significant trafficking of immune cells, such as natural killer (NK) cells and plasmacytoid dendritic cells (pDCs), from the periphery to the gut mucosa during infection [32,33]. Trafficking to the gut was associated with upregulation of α4β7 on NK cells and pDCs and blocking of α4β7 could reduce viral loads in this tissue [34].

Macaques infected with SIVmac exhibit all the different disease progression profiles described in HIV-1-infected humans, from rapid to slow progression. Spontaneous control of viral replication has been observed in at least two macaque species (rhesus and cynomolgus) with specific MHC or TRIM5 alleles [35–37]. Some SIVagm strains (SIVagm.ve90 and SIVagm. sab92018) induce AIDS in pig-tailed macaques, but not in rhesus macaques [38–40]. Infection of rhesus macaques with SIVagm.sab92018 is characterized by high levels of viraemia, and dramatic mucosal CD4+ T cell depletion during acute infection followed by complete control of SIVagm replication, defined as follows: undetectable viral load in the blood and tissues beginning at three months post-inoculation (pi) and continuing for at least 4 years; seroreversion; complete recovery of mucosal CD4+ T cells by 4 years pi; normal levels of immune activation; and no disease progression [39]. Virus control was independent of MHC, APOBEC and Trim5 genotypes. This ‘functional cure’ of SIVagm infection in rhesus macaques could be reverted by depleting CD8+ cells, which resulted in a transient rebound in viral load, suggesting that control may be at least partly immune-mediated. This represents a new animal model of controlled lentiviral infection, and other, complementary models are currently under development.

Macaque models are being used to examine the effect of short-term cART initiated at different stages during acute infection on viral dissemination and replication. The zidovudine/lamivudine and indinavir combination efficiently reduced...
viral replication in all tissues when treatment was initiated before peak viraemia. When the same treatment was initiated after peak viraemia, the effect of treatment was stronger in the gut than in the secondary lymphoid tissues [41]. Studies are currently being conducted to evaluate pre-exposure prophylaxis strategies such as rectal application of drug combinations before challenge [42].

Complete cART-associated suppression of SIVmac in rhesus macaques, even after several weeks and months of treatment, has been rarely achieved thus far. Without complete suppression, testing of strategies to reduce viral reservoirs is confounded by ongoing cycles of viral replication that can replenish such reservoirs. One major obstacle was the natural resistance of SIVmac to non-nucleoside reverse transcriptase inhibitors. Efforts are currently underway to achieve the goal of drug-induced full viral suppression in the macaque model, by improving drug combinations and administration strategies, and early results are encouraging [43]. Alternative strategies consist of chimeric simian–human immunodeficiency viruses, (SHIVs), in which the SIVmac reverse transcriptase (RT) is replaced with the RT from HIV-1 (RT-SHIV). RT-SHIVs have the advantage of being as susceptible to both nucleoside and non-nucleoside RT inhibitors as HIV-1. However, these chimeric viruses also have limitations; for example, the physiopathology of infection is not the same as with the wild-type virus. Recently, Shytai et al. [44] succeeded in completely suppressing viral replication by intensifying cART in SIVmac-infected rhesus macaques. Altogether, efficient treatment regimens in macaques will represent an essential model for answering crucial questions in the HIV cure research field, such as more precise insights into the nature of viral reservoirs in distinct body compartments during long-term treatment, the impact of early treatment on inflammation and viral reservoirs and the exact source(s) of virus during viral rebound.

Fundamental clues regarding the mechanisms that protect against AIDS also reside in the natural hosts of SIV, such as African green monkeys, sooty mangabeys (SMs) and mandrills [45]. In contrast to macaques, these African non-human primates are natural carriers of SIV in the wild. Protection against AIDS in natural hosts occurs despite viral replication in the blood and gut at levels similar to or higher than in HIV-1-infected humans and SIVmac-infected macaques [46]. Protection is associated with an absence of both chronic T cell activation and chronic inflammation [45,47]. The studies in natural hosts have contributed to the increased consideration of the major role of chronic immune activation in the development of AIDS. In countries where cART is accessible, the nature of HIV disease has largely shifted from one of immunodeficiency to one of chronic inflammation [48]. Deciphering the factors that predispose the natural host to control inflammation is the subject of several current studies and may have a major impact on translational research.

5. Insights into immune responses conferring spontaneous control of viral replication

HIV infection leads to a period of acute infection with vigorous viral replication, which is then partially controlled and stabilizes three to six months after infection. The pace and level of virus control depends on both viral and host determinants. Innate responses are mobilized to first counteract the virus and to assist in the development of adaptive cellular and humoral responses against HIV. However, these defences are generally imperfect and are eventually overwhelmed by the infection. Analysis of cases of immune-driven natural control of infection offers the opportunity to examine the characteristics of optimal immune function.

(a) Innate responses

(i) Natural killer cells

NK cells are key effectors of innate immunity. Through their capacity to mediate cytolysis and to produce numerous cytokines, NK cells can control the virus during the earliest stages of infection and shape the adaptive immune response. Thus, NK cells constitute one of the first lines of defence against HIV-1. Accordingly, several reports have linked enhanced basal and/or induced NK cell activity with protection from infection in groups of intravascular drug users, commercial sex workers and serodiscordant partners who remain seronegative despite repeated exposure to HIV-1 [49–53] (table 1). Once established, HIV-1 infection is accompanied by an expansion of NK cells [54]. However, a skewed distribution of NK cell subpopulations and loss of cell functions occur as a consequence of exposure to HIV-1 [55]. NK cell dysregulation is at least partially driven by viral products, which suggests that HIV-1 may have evolved to escape NK-cell-mediated control [56].

Evidence of a role for NK cells in the control of HIV infection comes from genetic and epidemiological studies. These studies consistently show that when linked with some HLA class I molecules carrying the Bw4-80I motif, some killer immunoglobulin-like receptor (KIR) (KIR3DS1/KIR3DL1) alleles are associated with low-level viraemia and slow disease progression [57,58]. The mechanisms underlying this control are not completely clear, but the interactions between KIR3DS1/KIR3DL1 and their Bw4 ligands may determine the expansion of specific subpopulations of NK cells [59] or the licensing of NK cells with increased responsiveness [60]. Recent studies suggest that changes in the peptides bound by HLA molecules may critically impact the way KIRs are stimulated by the HLA class I/peptide complex [61]. Interactions between KIR3DL1 and HLA class I alleles carrying the Bw4-80I motif are peptide-specific [62], and some peptide residues are directly involved in the binding of KIR3DL1 to its ligand [63]. Along these lines, compelling evidence of the impact of NK cells on virus control in the context of a particular KIR background comes from the observation that HIV-1 evolves to evade NK-cell-mediated immune pressure by selecting for sequence variants that specifically affect KIR binding to HLA class I ligands [64].

Natural control of HIV-1 infection appears to begin early in most HICs who usually have lower levels of viraemia than do progressor patients during acute infection [22]. The HLA-B alleles B*27 and B*57, which are commonly overrepresented in HICs [65–67], are members of the Bw4-80I group [68], suggesting that NK cells may contribute to establishing HIV control in these patients through direct cytolytic or non-cytolytic anti-HIV activities or by favouring the induction of an efficient CD8+ T cell response (see below) through optimal crossstalk with dendritic cells. Various reports suggest that NK cells from HICs have increased cytolytic and secretory potential [69–71], which may be associated with particular NK cell receptor profiles [69,71]. However, it remains unclear how this impacts the control of infection
in vivo, and NK cells from HICs exhibited only a modest capacity to suppress viral replication in autologous CD4+ T cells in vivo [72].

(ii) Plasmacytoid dendritic cells, type I interferon and intrinsic immunity

PDCs are another key component of the innate immune response. These cells influence HIV pathogenesis through their capacity to produce type I interferon (IFN-I) [73]. IFN-I upregulates interferon-stimulated genes (ISGs), several of which possess antiviral activity. During acute infection, pDCs may be a critical antiviral agent. IFN-α has long been known to block HIV-1 replication in vitro and in vivo [74–77]. Several studies performed during the past few years have identified a number of IFN-stimulated cellular factors (e.g. MX2, BST-2/tetherin, TRIM5α, APOBEC3G and SAMHD1) that can restrict retroviral replication [74,78–81]. During acute infection, transmitted founder viruses (HIV strains that succeed in establishing a persistent infection [82]) are more resistant to IFN-1 than chronic-phase HIV strains [83,84]. In addition to its antiviral effect, IFN-1 may also play an important role in the stimulation of innate responses (NK) and the shaping of adaptive immune responses [85].

By contrast, during chronic HIV infection, the continuous stimulation of pDCs may be deleterious via several mechanisms. The induction of inflammatory cytokines could enhance the trafficking of new target cells to sites of viral replication [86]. The IFN-mediated induction of indoleamine-pyrorrole 2,3-dioxygenase is associated with the loss of the TH17/Treg balance [87]. PDCs with increased TRAIL, another ISG, on their surfaces could induce apoptosis of DR5-expressing CD4+ T cells [88]. During a non-controlled HIV infection, the number of circulating pDC decreases, which is probably due to their migration to the lymph nodes and the gut where extensive HIV replication occurs [89]. By contrast, pDC levels in the blood of HICs are comparable to those found in normal donors and can produce high levels of IFN-α in response to HIV [90,91]. PDCs from HICs do not express TRAIL on their surfaces but carry high intracellular levels that can be mobilized to the membrane upon encountering HIV [90]. These results suggest that pDCs from HICs may specifically produce IFN-α and induce the apoptosis of infected cells [90,91]. Along these lines, pDCs from HICs can limit HIV replication in vitro when co-cultured with infected cells [91].

Other IFN-α-independent cellular factors can also block viral replication (e.g. p21) [92]. Host cells appear to have evolved a number of restriction factors that can block infection at different stages of the viral replication cycle. Many of these factors, which probably play critical roles in preventing cross-species transmission [93], are counteracted by HIV-1 proteins [94]. However, it is tempting to speculate that interindividual differences in expression levels and/or polymorphisms in these cellular factors may have an impact on HIV pathogenesis. Studies examining this question have produced conflicting results thus far. Polymorphisms in the Trim5α gene [95] and different expression levels of APOBEC3G [96] are associated with greater control of infection. However, this result has not been confirmed by other studies [97,98], and the expression of IFN-induced restriction factors may also be driven by viral replication [99]. Nevertheless, intrinsic cellular resistance to infection (e.g. linked to lack of CCR5 expression, high p21 levels) has been associated with both protection from infection among HIV-exposed seronegative individuals [100,101] and control of infection among HICs [102,103].

(b) Adaptive cellular responses

(i) CD8+ T cell responses

CD8+ T cell responses have been consistently associated with control of infection following acute HIV infection. The appearance of HIV-specific CD8+ T cells coincides with a decrease in viraemia during primary infection [104], and the selection of viral escape mutants in regions targeted by these responses [105]. CD8+ T cell responses targeting HIV-1 Gag epitopes are associated with smaller viral loads [106,107], which may be associated with a higher fitness cost for the virus to escape from Gag-restricted responses [108]. In vivo depletion of CD8+ cells in macaque models of pathogenic SIV infection has demonstrated that CD8-depleted macaques are unable to control infection during acute infection [109,110]. CD8+ depletion also results in increased viral loads in chronically infected macaques [111,112]. CD8+ T cells can counteract HIV by non-lytic (secretion of soluble factors such as β-chemokines or the as yet unidentified cellular antiviral factor) [113,114] or lytic mechanisms (cytolysis of infected cells through the Fas–Fas ligand pathway or cytotoxic granules) [115,116]. However, CD8+ T cells can only partially control HIV. Continuous HIV replication provokes the gradual loss of CD8+ T cell functions associated with the expression of negative regulatory molecules, such as PD-1 [117]. In addition to progressive CD8+ T cell exhaustion, HIV infection is characterized by a skewed distribution of HIV-specific CD8+ T cells with low frequencies of effector cells that may be especially prone to apoptosis [118,119].

Owing to the enrichment of protective HLA class I alleles among HICs, these individuals were soon proposed as a convenient model to uncover the characteristics of efficient CD8+ T cell responses against HIV-1. Despite the low levels of circulating virus in HICs, high frequencies of HIV-specific CD8+ T cells have been observed in these individuals [67,120]. These cells have maintained their capacities to proliferate in the presence of HIV antigens and to secrete IL-2 and other cytokines and chemokines [121,122]. Moreover, HIV-specific CD8+ T cells in HICs have been reported to possess or rapidly upregulate cytotoxic granule contents [123,124], and accordingly have a striking capacity to eliminate infected autologous CD4+ T cells [67]. This enhanced capacity to suppress HIV infection is linked to a higher frequency of further differentiated cells in association with a discordant CD38low/HLA-DRneg phenotype [67]. HIV-specific CD8+ T cell responses in HICs preferentially target epitopes in Gag, and Gag-specific responses account for most of their capacity to suppress HIV infection [125], which may be due to faster recognition of infected cells [126].

Some of the characteristics of HIV-specific CD8+ T cells from HICs are not found in most HIV-infected patients, even during primary infection [127]. Metabolic alterations in HIV-specific CD8+ T cells have been proposed to occur very early during acute infection owing to hyperproliferation associated with continual stimulation of the cells [128]. CD8+ T cells from HICs may also possess particular intrinsic characteristics. For example, selection of particular high-avidity TCR clonotypes associated with a broader capacity to recognize epitope variants and to orchestrate enhanced cytolytic functions has been shown to distinguish HICs from viremic HIV-infected patients sharing the same protective HLA class I alleles [129,130]. Selection of such clonotypes occurs very early,
although the mechanisms of selection are unknown. The function of myeloid dendritic cells, which are principally responsible for priming T cell responses, is altered during primary infection [131] (blood). By contrast, myeloid dendritic cells from HICs have enhanced antigen-presenting capacities, but produce lower levels of pro-inflammatory cytokines [112] and our own unpublished data, 2013). This profile may favour T cell priming and the selection of specific optimal clonotypes in the context of reduced antigenaemia and a weakly inflammatory environment.

During the chronic phase of infection, instead of a strong effector CD8+ T cell response, many HICs present with a small number of quiescent memory CD8+ T cells [125,133,134]. These responses may constitute a pool of preserved CD8+ T cells that are highly reactive to small quantities of antigen and can rapidly gain effector capacities in response to viral relapses from HIV reservoirs. This hypothesis is supported by in vitro experiments in which memory CD8+ T cells from these HICs were able to gain cytotoxic activities within a few days of stimulation with cognate peptides [135]. These experiments are not completely conclusive, because cells from non-controller patients also gain anti-HIV capacities upon stimulation in vitro [136]. Therefore, further studies are necessary to identify clear distinguishable characteristics in memory CD8+ T cells from HICs, which may hold important clues for the development of an efficient T-cell-based vaccine.

(ii) CD4+ T cell responses

CD4+ T cells play a multifaceted role in HIV infection. CD4+ T cells provide crucial help to dendritic cells and B cells for the induction of HIV-specific CD8+ T cells and antibodies. Furthermore, CD4+ T cells are the main cellular target of HIV, and HIV-specific CD4+ T cells are preferentially infected by the virus [137]. Induction of activated HIV-specific CD4+ T cells in vaccine trials has been associated with a higher risk of HIV infection [138] or with faster viral rebound in HIV-infected individuals upon interruption of treatment [139]. By contrast, induction of HIV-specific CD4+ T cell responses was not associated with an increased risk of infection in the RV144 vaccine trial [140], and higher frequencies of HIV-specific CD4+ T cell responses during primary infection have been associated with higher CD4+ T cell counts and lower viral loads after short-course antiretroviral treatment [141]. Moreover, several studies have shown that some HIV-specific CD4+ T cells develop cytolytic potential and carry high levels of granzyme A [142,143]. These cells may be able to eliminate infected macrophages and, to a lesser extent, activated CD4+ T cells expressing high levels of HLA class II molecules [142]. A recent study linked high levels of cytotoxic HIV-specific CD4+ T cells during acute infection with lower set-point viraemia, supporting a direct effector activity for this subset of HIV-specific CD4+ T cells [144].

In general, primary HIV infection is accompanied by the depletion of HIV-specific CD4+ T cells and impaired cell functionality, particularly the capacity to proliferate and produce IL-2 [145]. As was the case for CD8+ T cells, in HICs, HIV-specific memory CD4+ T cells maintain their functionality [146–148]. High-quality memory CD4+ T cells in HICs have been associated with reduced expression of the negative immunoregulatory molecule cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [149] and lower levels of FoxO3a-mediated pro-apoptotic transcriptional activity [150]. HIV-specific CD4+ T cells from HICs also exhibit high avidity for immunodominant Gag peptides, which may allow them to react to low levels of antigens [151]. The class II HLA alleles HLA-DRB1*13 and HLA-DQB1*06 have been associated with strong HIV-specific CD4+ T cell responses in HICs [152].

CD4+ follicular T helper (Tfh) cells, which regulate the development of antigen-specific B cell immunity, have received special attention in the past couple of years. Tfh cells are highly susceptible to HIV-1 infection in vitro and are a major site of viral replication and a viral reservoir [153,154]. Tfh cells are infected at higher frequencies in macaques and humans than in Sm [155]. In contrast to most other CD4+ T cells, this subset is expanded and accumulates in lymph node germinal centres during HIV and SIVmac infections [153,156–158]. Whether Tfh in HIV infection shows an altered function that could impact anti-HIV antibody development is unclear.

Regulatory CD4+ T cells (Tregs) may play a dual role in HIV pathogenesis. Tregs may contribute to reduced pathogenesis by controlling chronic immune inflammation but may facilitate infection by suppressing the activation of effector T cells [159]. During HIV infection, Tregs accumulate in the gut [160]. The ratio of Treg:TH17 cells decreases, and this imbalance may have a deleterious effect on the integrity of the gut mucosa [161]. In contrast to other effector CD4+ T cell subsets, Tregs preserve their suppressive capacity despite HIV-1 infection [162]. HICs appear to maintain similar or lower levels of Tregs than do healthy individuals [162–165], and their CD8+ T cells may evade Treg-mediated suppression [166]. This mitigated regulatory response in HICs may help to maintain a robust and efficient T cell response but may also explain the relatively high immune activation observed in these individuals [163], which is associated with some loss of CD4+ T cells (see §6).

(c) Humoral responses

HIV infection elicits an antibody response that targets HIV envelope protein and is non-neutralizing during the early stages of infection. Neutralizing antibodies are only generated months after infection is established and usually lag behind viral escape mutants [167]. A blunted antibody response during HIV infection is associated with B cell dysfunction. Some individuals, elite neutralizers, can elicit broadly neutralizing antibodies that recognize conserved regions of the virus envelope protein [168]. The presence of these broadly neutralizing antibodies is not associated with a dramatic control of viraemia in vivo, but has been shown to strongly decrease viraemia when administered to SHIV-infected macaques [169]. Neutralizing IgAs have been found in the genital tract of different cohorts of highly exposed but seronegative females [170,171], suggesting that these antibodies contribute to protection from AIDS acquisition in these subjects.

High levels of IgG2 antibodies targeting gp41 were reported as a strong correlate of slow progression to AIDS [172], and these antibodies are also found at high levels in HICs [173,174]. The mechanism through which these antibodies contribute to HIV control is unknown, although it seems to be unrelated to direct neutralization. In general, HICs possess heterogeneous but low levels of neutralizing antibodies, suggesting that they are not a major determinant of virus control [134,175]. By contrast,
greater antibody-dependent cell-mediated cytotoxicity (ADCC) potential associated with both the quality of non-neutralizing antibodies and the levels of Fcγ receptors on the surface of effector cells has been observed in HICs [17,175–177]. The induction of ADCC-mediating antibodies was observed in vaccinated volunteers in the RV144 vaccine trial [178], showing marginally significant protection from HIV infection [179] and further reinforcing the potential therapeutic utility of ADCC.

Additional antibody-related activities may impact HIV infection. Non-neutralizing antibodies form immune complexes with soluble HIV antigens that stimulate Fcγ receptors expressed by myeloid cells, particularly macrophages. Fcγ receptor aggregation provokes a blockade of viral replication through the induction of p21 and the alteration of the de novo synthesis pathway of dNTPs, which are necessary for the reverse transcription step of viral replication [92,180]. By contrast, anti-HIV antibodies may compete with complement to opsonize viral particles. The complement system is part of the innate immune response that is activated immediately upon HIV-1 infection. Among other activities [181], complement opsonization of viral particles has been shown to favour HIV-1 capture and uptake by dendritic cells [182], which is associated with enhanced intracellular co-localization of HIV antigens with HLA class I molecules and effective CD8+ T cell priming by dendritic cells. This effect is gradually lost with the deposition of HIV IgG on viral particles [183]. In summary, further studies need to be conducted to understand the impact of non-neutralizing antibodies in vivo.

6. Spontaneous control of chronic inflammation in HIV/SIV infections

The proportion of infected CD4+ T cells is too small to fully account for the extent of CD4+ T cell decline. Many data points towards systemic immune activation as the factor responsible for HIV-induced immunodeficiency [12]. Indeed, studies on HIV-2 infection and in natural hosts indicate that viral replication alone is not sufficient to induce AIDS. Many studies have demonstrated that inflammation is even more closely associated with mortality in HIV-infected patients than T cell activation. Therefore, inflammatory and coagulation biomarkers (highly sensitive C-reactive protein (hsCRP), IL-6 and D-dimers) are associated with immunological failure, clinical events and AIDS- and non-AIDS-related mortality [11].

(a) Natural control of inflammation in the context of high-level viraemia

Natural hosts exhibit spontaneous protection against chronic immune activation despite high levels of viraemia, high mucosal replication and dramatic CD4+ T cell loss in the gut [46]. During the chronic phase of infection, peripheral and tissue T cell activation levels are not or are only modestly increased. No elevation in the expression of inflammatory cytokines is observed [46]. There are no increases in coagulation markers such as D-dimers [184]. A lack of chronic immune activation is observed despite an initial transient activation or mobilization of pDCs, myeloid dendritic cells (mDCs), NK cells and T cells [185–187]. Indeed, the acute phase of SIVagm infection is characterized by the recruitment of pDCs and mDCs to the lymph nodes, IFN-α production, induction of ISGs and corresponding protein expression.

Early inflammation may be essential for both the virus and the host. Inflammation would be beneficial to the virus, because it attracts target cells to the site of infection and would allow the virus to establish a persistent infection. For the host, the induction of early innate antiviral responses (including IFN-α) would allow partial control of viral replication. Inflammation would then be resolved before the end of acute infection. For example, most ISGs are downregulated back to normal levels in natural hosts in contrast to pathogenic HIV/SIVmac infection [46]. The lack of chronic inflammation would prevent immune-mediated pathology and disease progression.

However, there are major differences compared with SIVmac infection in macaques: the levels of several cytokines, including IFN-α, are lower than those observed during acute SIVmac infection, which is not due to a functional defect in the ability of pDCs to sense the virus [188,189]. Indeed, the TLR7/TLR9/IRF7 pathway is functional [188,189]. In addition, natural hosts preserve their TH17 cells, and their epithelial barriers are not damaged and consequently they show no signs of microbial translocation. This could at least partly explain the lack of systemic immune activation during the chronic phase. Finally, several differences in viral reservoirs in natural hosts with respect to HIV-1 and SIVmac infections have been reported: a smaller DNA reservoir (PBMC), less replication in the lymph nodes, less infection of CD4+ TCM, no infection of Tcm, and no or rare trapping by follicular dendritic cells [46,190]. The relevance of these observations to the lack of AIDS requires further investigation, but it is interesting to note that small reservoirs and low contribution of Tcm cells have been associated with control of HIV infection in BS7-bearing non-progressor patients and also in PTCs from the VISCONTI study [17,191].

Similar to natural SIV hosts, VNPs do not control viral replication but nonetheless maintain close to normal CD4+ T cell counts for many years in the absence of treatment. The maintenance of CD4+ T cells is associated with a low frequency of activated (DR+CD38+) and proliferating (Ki-67+) CD4+ and CD8+ T cells [192]. Therefore, attenuated infection is equally associated with a lack of chronic immune activation. Obviously, a functional cure such as in VNPs (or natural hosts) without control of the virus is less attractive because of the risk of viral transmission. However, it is crucial to understand how VNPs avoid chronic immune activation. VNPs are rare, and unfortunately only limited information on their immune responses is available.

(b) Inflammation and CD4+ T cell loss in HIV controllers

HICs can experience modest CD4+ T cell loss despite controlled viraemia. Higher CD4+ and CD8+ T cell activation is associated with a progressive loss of CD4+ cell counts in HICs [193]. CD8+ T cell activation levels in HICs are also higher than in healthy donors, efficiently treated aviremic patients [193] and PTCs. Higher levels of sCD163, sCD14, IP-10, TNF-α, sTF, D-dimers and hsCRP as well as an increased risk of atherosclerosis have been observed in some HICs compared with healthy donors or aviremic treated patients [194–197]. HICs also seem to have elevated levels of microbial translocation compared with HIV-negative
and cART-suppressed individuals [163]. In a recent study, the relationship between inflammatory biomarkers and the CD4+ T cell decreases observed in some HICs has been investigated in a large HIC cohort [197]. In this study, IP-10 positively correlated with activated CD8+ and CD4+ T cells in HICs. Moreover, IP-10 and sCD163 levels in HICs predicted the risk of CD4+ decline. Therefore, the association between inflammation and disease progression is similarly present in HICs as in other HIV-infected individuals [11,13].

It is unclear what drives chronic inflammation in HICs despite the control of viral replication, but it could be associated with extremely low but continuous HIV replication over several years. Very low plasma levels of virus can be detected by ultrasensitive RT-PCR assays in HICs, revealing the persistence of viral replication despite maintaining viraemia close to the limit of detection by standard RT-PCR [198]. Although HICs maintain a remarkable control of infection, blips in viral load levels have been observed for many of these individuals [199]. By contrast, some HICs never experience blips, even over long follow-up periods and when using ultrasensitive techniques that detect 1 RNA copy ml−1 of plasma. Interestingly, these HICs are similar to healthy individuals from a transcriptomic point of view [200]. HICs with blips more often exhibit CD4+ T cell loss [199]. Moreover, theoretically, chronic low-level inflammation in HICs could also be driven by higher viral replication in a few as yet unidentified sanctuaries. Such sanctuaries could correspond to immune-privileged compartments in the body, such as the brain. Recent studies in the macaque model suggest that this sanctuary could also be represented by T FH cells in germinal centres (GCs) [201]. In late-stage HIV infection, GCs are characterized by infiltration of CD8+ T cells [202]. However, under normal conditions, GCs are devoid of CD8+ T cells. Theoretically, GCs could represent a compartment in the body where HIV could evade control by CD8+ T cell responses and replicate to higher levels than in the remaining lymph nodes and mucosal tissue cells. Finally, because most HICs have been infected for long periods, lymphoid tissues might represent some of the damage described in normal progressors, such as disruption of the epithelial barrier leading to translocation of microbial products. Indeed, HICs show increased levels of microbial translocation markers [197]. Translocation of microbial products into systemic circulation could then fuel immune activation. Studies in the non-human primate model have provided the proof of concept that higher systemic lipopolysaccharide (LPS) levels lead to increased T cell activation [203], which could reactivate latent virus, leading to a vicious cycle.

7. Hopes and future directions for a cure

An HIV cure will succeed by targeting viral reservoirs, but in vitro and in vivo evidence suggests that host immunity should be targeted concomitantly. Very small viral reservoirs are most likely necessary but not sufficient to ensure the control of viraemia off treatment, and the induction of efficient responses against HIV, eventually combined with anti-inflammatory approaches, will be necessary to eliminate HIV-producing cells in reservoir-purging protocols (see [204] for further information on current HIV cure strategies). Several novel treatment approaches to improve host immune responses are currently under investigation.

(a) Early treatment interventions

Although current antiretroviral strategies seem to have reached their limits in terms of blocking HIV replication, early treatment initiation may provide further advantages. As previously described, treatment initiation during primary HIV infection has been linked to lasting remission of HIV infection in a group of adults [17]. Treatment initiation immediately after birth also allowed a functional cure of HIV infection in a child after treatment discontinuation [205]. Early treatment limits the establishment of viral reservoirs [206] and severely restricts viral diversity [207]. In addition, treatment initiation during primary infection has been shown to preserve CD4+ T cell homeostasis and the function of NK cells, B cells and HIV-specific T cells [95,145,208]. Therefore, early treatment may allow an optimal maturation of the anti-HIV response by reducing viraemia and inflammation, which may favour the control of infection after treatment interruption in some individuals with low levels of infected cells. Larger studies need to be performed to identify the mechanisms associated with control after treatment interruption and to uncover predictive markers of post-treatment control.

(b) Immunotherapies

Immunotherapies based on the administration of IL-2, IL-7 or IL-15 alone or in combination with vaccine candidates aim to enhance immune function and restore T cell homeostasis [209]. IL-7 has garnered some interest [210,211], but it increases the number of infected cells [210,212], and thus far these approaches have not shown sufficiently favourable effects in vivo.

Treatment with IFN-α has been shown to transiently decrease viral loads during chronic infection [74,213], and IFN-α monotherapy was recently shown to allow control of viraemia and reduction of viral reservoirs after antiretroviral treatment interruption in 48% of individuals who received IFNα for several weeks in addition to their HIV-suppressive cART regimens [214]. The mechanisms underlying this effect are still unclear, but as discussed above, IFNα treatment may enhance the immune response in treated individuals and also upregulate HIV restriction factors, thereby rendering target cells less susceptible to HIV infection. Nevertheless, IFNα therapy requires further exploration, because conflicting results have been obtained depending on whether it is administered in the absence or presence of cART or in patients with very low CD4+ T cell nadirs [20,215].

The observation that exhaustion of HIV-specific T cells is accompanied by enhanced expression of negative immunoregulatory molecules such as PD-1 has nurtured the hypothesis that targeting these immunomodulatory pathways may be a promising therapeutic approach in the fight against HIV (reviewed in [216]). In vitro, blockade of PD-1 interactions with PD-1 ligands restores CD4+ and CD8+ T cell functions, particularly proliferation and cytokine production. Proof-of-concept studies on SIV-infected macaques have shown that PD-1 blockade results in the expansion of CD8+ T cells with improved functionality [217], longer survival and decreased viral loads in infected animals [217] and may delay viral rebound after treatment interruption [218]. Anti-exhaustion strategies may not restore HIV-specific T cell functions to the levels found in HICs, because some intrinsic characteristics of HIC cells are determined very early during infection (see above). However, the restoration of partial T cell function may act in synergy with additional effects of these strategies.
PD-1-expressing cells are preferential targets of HIV-1 infection [219]. Furthermore, the PD-1 pathway has been linked to the establishment of HIV latency, and triggering PD-1 may help to purge HIV-1 reservoirs. Moreover, in vivo PD-1 blockade also produces a reduction of the immune activation associated with chronic SIV infection [220].

(c) Anti-inflammatory therapies

Because immune activation is a major determinant of HIV pathogenesis, direct targeting of deleterious inflammation is increasingly attracting attention. Many assays are currently under investigation [221]. Chloroquine analogues are among the first anti-inflammatory molecules assessed in HIV-infected patients [222,223]. The rationale behind this approach is that chloroquine can inhibit the recognition of HIV via TLR7 and TLR9 [224]. Although one study showed that short-term chloroquine administration during chronic infection in a small group of cART-naive patients resulted in a reduction in T cell activation markers in the absence of changes in plasma viremia [225], a randomized double-blind trial with a larger group of HIV-infected patients demonstrated that longer hydroxychloroquine administration resulted in faster CD4 T cell decay and some increase in viral replication [226]. PD-1 blockade during chronic SIV infection markedly reduced the expression of transcripts associated with type I IFN signalling in the blood and colorectal tissue of rhesus macaques, even in the presence of high levels of viremia [220]. Reduced type I IFN signalling was associated with a profound decrease in plasma LPS levels, suggesting decreased microbial translocation into the blood. PD-1 blockade enhanced immunity to gut-resident pathogenic bacteria, control of gut-associated opportunistic infections and survival of SIV-infected macaques. The effects of PD-1 blockade on reducing hyperimmune activation could be a combination of enhanced immunity against gut-resident pathogenic bacteria and repair of gut barrier permeability.

Statin administration to HIV-infected patients has been shown to reduce inflammation [227] and may decrease the risk of non-AIDS-defining malignancies [228] and comorbidities [229]. By contrast, statins may increase the risk of developing diabetes [230]. Studies with other anti-inflammatory agents (non-steroidal anti-inflammatory drugs, pyridine synthesis inhibitors, probiotics and cyclooxygenase-2 inhibitors) have revealed similarly contrasting results. Other trials with anti-inflammatory agents, such as anti-IL-6 and JAK inhibitors, are planned or are underway [231]. In conclusion, clinical trials have thus far shown that identification of the factors responsible for chronic inflammation is needed to be able to develop more specific, better targeted approaches.

Administration of cART on its own reduces inflammation, in a large part through the reduction of viral replication [232]. The effect of early cART treatment on inflammation was assessed more recently [233]. In a pilot study, Mega-cART initiated during acute infection resulted in the reduction of viral reservoirs down to 100 copies of viral DNA per 10^6 CD4 T cells at six months pi (M6). In parallel with the decrease in the viral reservoir, some inflammatory markers were reduced, including IP-10 and D-dimers at M6, whereas LPS and sCD14 were not. In another study in which treatment was also initiated during acute infection, the plasma levels of IP-10 were decreased, whereas those of 12 other cytokines studied were not [234]. Therefore, early treatment seems to diminish inflammation to some extent. It is not clear why the effect was only observed for some inflammatory markers but could be because they are more closely associated with replication levels or earlier and better markers of inflammation [13]. Intensiﬁcation treatment in cART-suppressed individuals may help to further reduce residual viral replication and immune activation. Early intensiﬁcation of treatment with the CC chemokine receptor 5 (CCR5) antagonist maraviroc may be of special interest not only because the viruses that are capable of establishing an infection generally use CCR5 as a co-receptor, but also because of the quick penetration and sustained concentrations of maraviroc in the rectal mucosa [235]. The addition of maraviroc to the antiretroviral regimen resulted in a faster reduction in newly infected cells [236], a decrease in microbial translocation markers [237,238] and a faster increase in CD4 counts [236,237]. Paradoxically, maraviroc also induced a slower decrease in plasma viraemia. It has been suggested that this result may be due to an immunoactivatory effect of maraviroc. Indeed, MIP1b levels, CD8 T cell counts and CD4 T cell activation were higher in the maraviroc arm of the study [236,237]. However, higher T cell activation levels were not observed in another study [238]. In an uncontrolled trial of maraviroc intensiﬁcation, plasma LPS levels were actually increased [237], and soluble inﬂammation markers were similar in both arms at the end of the study [236].

It has long been assumed that HICs do not need cART owing to their ability to efﬁciently control viral replication. In the light of the higher levels of immune activation among HICs than patients on cART, it has recently been questioned whether cART could be beneﬁcial to HIC patients. A recent pilot study comprising a small number of HICs assessed whether cART leads to a reduction in inﬂammation in HICs [239]. Antiretroviral therapy in these HICs led to statistically signiﬁcant decreases in ultrasonic plasma HIV RNA levels and rectal cell-associated HIV RNA as well as decreased T cell activation levels (DR+CD38+) in both the blood and gut. This pilot study suggests that even low-level replication results in immune activation. Larger studies will be needed in the future to test whether the reduction in immune activation observed has any clinical relevance for HICs.

(d) Therapeutic HIV vaccines

The quest for an effective HIV vaccine has been unsuccessful thus far. Different vaccine candidates have been evaluated in six phase III clinical trials. Most candidates did not show any efﬁcacy, and the STEP and HVTN503 trials showed an increased risk of HIV acquisition in vaccinated individuals (http://www.hvtnc.org/media/pr/step111307.html). The HVTN 505 trial was also recently interrupted for futility (http://www.niaid.nih.gov/news/newsreleases/2013/Pages/HVTN505April2013.aspx). Only the RV144 trial showed marginal efﬁcacy [179]. Although a clear correlation of protection has not been identiﬁed for this trial, vaccination was associated with the induction of ADCC-mediating antibodies [178]. Overall, conventional HIV vaccine development has been disappointing, and an efﬁcient therapeutic HIV vaccine will probably require innovative approaches.

Dendritic cell-based vaccines have garnered special attention in recent years. One approach consists of vaccinating HIV-infected patients using autologous inactivated viruses to pulse dendritic cells derived from autologous monocytes.
The observation that passive transfer of broadly neutralizing antibodies allows for the control of infection in chronically SIV-infected macaques [169] and delays viral rebound in acutely treated patients after cART cessation [245] suggests that a therapeutic vaccine that induces broadly neutralizing antibodies may be effective for controlling HIV-1 in infected patients. Recent knowledge of the coevolution of the viral epitopes and neutralizing antibodies [246] might prove critical to anticipate the time-course that would be established between the virus and the immune system after an eventual treatment interruption. However, inducing such antibodies by vaccination remains a challenge. Current efforts are aimed towards identifying the structural characteristics associated with the neutralizing efficacy of broadly neutralizing antibodies that target major sites of vulnerability in the envelope protein [247], the events that lead to their production [248] and the B cell clones that express their germline precursors [249,250], as well as towards designing mosaic antigens that elicit broad responses [251].

In conclusion, studies of natural protection against HIV/AIDS have already provided important clues about protective host determinants. Analyses of the immune responses functioning in these models offer signatures or correlates of protection that will then need to be validated in translational research. However, many questions remain to be investigated, such as the mechanisms of residual replication, the factors driving chronic immune activation and the mechanisms underlying treatment-induced protection against viral replication. In future, such insights will be helpful to design efficient, well-targeted strategies for a cure and may also be of use for vaccine strategies.

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