HIV-1 elite controllers: an immunovirological review and clinical perspectives

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Abstract

HIV type 1 (HIV-1) elite controllers (ECs) represent a rare group of individuals with an ability to maintain an undetectable HIV-1 viral load overtime in the absence of previous antiretroviral therapy. The mechanisms associated with this paradigm remain not clearly defined. However, loss of virological control, morbidity and mortality persist in these individuals, such as progress to AIDS-defining conditions together with persistent high rate of immune activation. Further insight into potential therapeutic options is therefore warranted. In this review, we discuss recent data on the type of immune responses understood to be associated with chronic virological control, the potential for disease progression and therapeutic options in ECs.

Introduction

Several years after the discovery of the HIV type 1 (HIV-1), a small subset of individuals was identified with a rare ability to spontaneously maintain an undetectable viral load (VL) in the absence of previous or ongoing antiretroviral therapy (ART). Various definitions have been applied to these individuals, known as elite controllers (ECs) [1,2]. However, some of them may lose virological control and progress overtime both virologically and also clinically to AIDS-defining conditions.

The subset of ECs was further distinguished from viraemic controllers (VCs) and long-term non-progressors (LTNPs) primarily on the basis of their VL level. Compared with VCs and LTNPs, ECs represent a smaller subset of less than 1% of all individuals with HIV-1 [1–4]. Their spontaneous virological control should be ideally replicated more widely in HIV-1-positive individuals and is therefore of great research interest. However, the mechanisms underlying virological control remain [5]. Furthermore, because of their potential for clinical progression in this population, there have been questions asked recently regarding the need for treatment initiation even when virological control was present.

In this review, we shall describe the various immunovirological mechanisms that have been suggested as supporting the EC phenotype and review the various therapeutic options in this group of ndividuals.

Mechanisms of spontaneous HIV-1 control

Various hypotheses have been put forward to explain the spontaneous virological control as seen in ECs. These include defective HIV-1 variants, innate resistance to HIV-1 infection, limited availability of susceptible $CD4^+$ T cell targets and an immune-based control of viral replication. Most studies have concluded that ECs control the infection via virus-specific T cell-mediated immune responses, which differ from non-controllers in a number of ways [3,6]. Human leukocyte antigen (HLA) class I, $CD8^+$ T lymphocytes/cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells have also been implicated. In addition, follicular helper T cells, HIV-1 antibody responses and certain patterns of cytokines and biomarkers have recently been shown to be associated with virological control. In contrast, factors such as low *gag*-specific T cell polyfunctionality, high viral diversity and pro-inflammatory cytokines levels, including RANTES, have been described before loss of virological control [7,8].

Human leukocyte antigen

The HLA system or complex is a gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system. The HLA class I molecules are predictive of the course of HIV-1 infection [9]. They are expressed by most human cells, divided into HLA-A, HLA-B and HLA-C classes and present antigens to $CD8^+$ T cells, leading to their activation and, in the case of HIV-1, to the destruction of infected cells [10].

However, the viral nef protein has a role in immune evasion by disrupting antigen presentation at the cell surface of infected cells through MHC-1 downregulation of class I HLA-A and HLA-B, thereby decreasing CTL recognition and cell lysis [9,11]. It is thought to represent a mechanism through which HIV-1 can simultaneously avoid NK cell cytotoxicity and CTL detection [12].

Several alleles of the MHC class I genes have been found to show a correlation with delayed progression in ECs controlling VL. According to a study by Rajapaksa *et al*., HLA-B may be more protective against HIV-1 infection compared with HLA-A due to its ability to resist *Nef*-mediated downregulation [13]. Certain HLA-B alleles such as *B*27*, *B*57* and *B*14*, which are prevalent among ECs, were found to be associated with enhanced virological control among these individuals [14–16] . Using a whole genome-wide association study, Fellay *et al*. have identified 15 polymorphisms that explained the nearly 15% variation in VL during the asymptomatic phase of the infection, such as HLA-B5701 and another located close to the HLA-C gene [16]. Two genes are associated with time to disease progression [16]. One encodes an RNA polymerase I subunit. Pereyra *et al*. have also performed a genome-wide association analysis in a multiethnic cohort of ECs and progressors and analysed the impact of individual amino acids within the classical HLA proteins [15]. More than 300 genome-wide significant single-nucleotide polymorphisms were identified within the MHC. As specific amino acids in the HLA-B

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peptide-binding groove were associated with both protective and risk HLA alleles, the HLA type and viral interaction were shown to be major determinants of durable virological control, with those individuals with HLA-B27 having more efficient polyfunctional CD8+ T cell responses. Almeida *et al*. have shown that B27-KK10-specific CD8+ T cells are characterised by increased clonal turnover, superior functional avidity and polyfunctional capabilities, which contribute to the effective control of HIV-1 replication [14]. Betts *et al*., however, have described that enhanced functionality in non-progressors was not associated with the presence of HLA-B57 as presenting allele [17].

CD8+ T cells and natural killer cells

The CD8+ T cells in ECs were found to be qualitatively superior compared with those of progressors. This was attributed to their polyfunctionality, as characterised by an efficient degranulation process and release of perforin and granzyme B, in addition to cytokine secretion (interferon [IFN]-γ, tumour necrosis factor [TNF]-α, interleukin [IL]-2 and macrophage inflammatory protein [MIP]-1β). Similarly, when Betts *et al*. assessed CD8+ T cell functions (degranulation, IFN-γ, MIP-1β and TNF-α), they found that the HIV-1-specific CD8+ T cell functional profile in progressors was limited compared with that of non-progressors. Non-progressors produce little TNF-α and even less IL-2, unlike progressors [17]. This limited functionality was found to be HIV-1-specific, independent of a T cell memory phenotype and HLA type, and refractory to therapeutic intervention. In the same study, disease progression was correlated to the quality of the CD8+ T cell functional responses rather than to their quantity or phenotype [17].

Given that gut-associated lymphoid tissue is an important reservoir of lymphocytes as well as HIV-1 replication *in vivo*, some studies have compared CD8+ T cell responses in blood and mucosal tissue [18,19]. With few exceptions, an extensive overlap was found in both compartments [18,19]. Responses to HLA-B27- and HLA-B57-restricted epitopes were found to be similar in blood and mucosa in ECs [18]. The magnitude of responses was significantly greater than that restricted by other alleles, and this was especially true for the *gag*-specific ones targeting p24 and p27 in both compartments [18]. In terms of magnitude and breadth, HIV-1-specific *gag* responses were dominant in ECs, while progressors showed an even distribution among various epitopes (*gag*, *env* and *nef*) [18].

The NK cell population has been implicated in the ECs' ability to control virological replication as a result of their cytotoxic activity against infected cells. These cells and a minority of T cells express a family of type I transmembrane glycoproteins known as killer inhibitory receptors (KIRs), which interact with MHC class I molecules to regulate their killing function [20]. According to Genovese *et al*., KIR3DS1 and KIR3DL1, when interacting with HLA-B alleles, are associated with delayed disease progression in cohorts of HIV-1-positive individuals with spontaneous control of VL [3]. The HIV-1 controllers expressing *HLA-Bw4*801* on target cells and KIR3DL1 on NK cells displayed a stronger target cell-induced NK cytotoxicity compared with CD8+ T cells of the same individuals [3].

Further potential immunological mechanisms

According to Hunt *et al*., ECs have higher CD4+ and CD8+ T cell activation levels compared with individuals without HIV-1 and higher CD8+ T cell activation than individuals on ART [21]. This was associated with lower CD4+ T cell counts as it appeared to be responsible for the progressive loss observed in some ECs [21]. This assumption was, however, refuted by two studies. Yang *et al*. have shown that most ECs were able to preserve normal total CD4+ T cells when thymic and extrathymic processes remained intact [2]. Similarly, Kamya *et al*. have found no association between elevated immune activation and rate of CD4+ T cell decline when using CD38+HLA-DR+CD8+ T cell measurements [22]. In another study by O'Connell *et al*., cells from ECs were as susceptible to *ex vivo* infection as those of individuals without HIV-1 but more susceptible than those of progressors [23]. In addition, HIV-1 was shown to target memory CD4+ T cells that are present in greater number in ECs than in progressors. In another study by Chen *et al*., CD4+ T cells from ECs were less susceptible to HIV-1 infection compared with progressors and individuals without HIV-1 [24]. This was associated with a strong, yet selective upregulation of the cyclin-dependent kinase inhibitor p21 and a less effective mRNA transcription from proviral DNA. Moreover, a marked increase of viral reverse transcripts and mRNA synthesis, as well as a higher enzymatic activity of cyclin-dependent kinase 9 (a transcriptional coactivator of HIV-1 gene expression), was observed following experimental p21 blockade in CD4+ T cells. It can be inferred that by inhibiting cyclin-dependent kinases needed for effective HIV-1 replication, p21 acts as a protective factor against infection, potentially leading to novel therapeutic interventions for the treatment and/or prevention of HIV-1 infection [24]. No difference in death rate of infected cells was found in ECs and progressors. O'Connell *et al*. have shown that the burst size was greater in progressors than in ECs, which might be one of the explanations in the difference in outcome between these two groups [23].

Differences in T follicular cells, as well as antibody responses between ECs and progressors, have recently been investigated [25,26]. HIV-1 *env* gp120 probes were employed to study HIV-1-specific B cell immunophenotypes in individuals with various levels of virological control [25]. The functionality of matched T cells in peripheral blood was then characterised. Despite having significantly decreased CXCR5+ CD4+ T cells, a small subset of *gp120*-specific IL-21-secreting cells were significantly associated with *gp120*-specific T cell frequencies in progressors. This association was lacking for bulk CXCR5+ CD4+ T cells or other HIV-1 antigen specificities [25]. HIV-1-specific B cells from ECs displayed greater amounts of *gp120*-specific B cells in the resting memory subset in comparison with progressors, where they were found to accumulate in tissue-like and activated memory subsets. In addition, CXCR5+ CD4+ T cells from ECs had a greater *ex vivo* capacity to induce immunoglobulin class switching, as well as B cell maturation than those from progressors [25]. It can be concluded that immune responses in ECs demonstrated an intrinsically superior helper activity than those of progressors.

Studies have aimed at analysing the factors involved in B cell maturation. Specific antibody responses in ECs have rarely been studied as it was thought that the titre of broadly neutralising antibodies was not higher than that in progressors. Nabi *et al*. [26] compared ECs' ability to generate high-quality HIV-1-specific IgA responses with viral suppressors or progressors on ART. Findings showed that ECs developed stronger IgA responses to the HR1 domain of *gp41*, higher avidity *gp41*-specific IgA antibodies and more frequent IgA responses to HIV-1 *gp160* compared with other groups of individuals living with HIV-1. Additional studies focusing on functional analysis of IgA antibodies are needed to better understand if and how these contribute to virological control.

The EC population was found to have a stronger and broader HIV-1-specific immune response with seven cytokines and chemokines (GM-CSF, TNF-α, IL-2, MIP-1β, IFN-γ, IP-10 and MCP-3) compared with non-controllers. They also had lower levels

of inflammatory markers, such as IL-10, MCP-1, albumin and neopterin. Moreover, unlike individuals on ART, ECs did not show increased T-reg cell numbers [27].

Jacobs *et al*. have identified higher expression levels of SDF-1, CCL14, CCL21, CCL27 and XCL1 in ECs in comparison with VCs, HIV-1-negative individuals or those on ART [28]. The combination of five cytokines was found to suppress R5 and X4 virus replication in resting T cells while upregulating CD69 and CCR5 and downregulating CXCR4 and CCR7 on $CD4^+$ T cells. It also induced the expression of IFITM1 and IFITM2 (anti-HIV-1 host restriction factors) and suppressed that of RNase L and SAMHD1. This study identified elevated cytokines in ECs and their impact on cellular activation and HIV-1 coreceptor and innate restriction factor expression.

Ongoing chronic immune activation in ECs has been demonstrated in various studies compared with virally suppressed HIV-1-positive individuals on ART [29–32]. Hunt *et al*. have shown higher $CD8^+$ T cell activation and lipopolysaccharide (LPS) levels in ECs than in HIV-1-negative individuals [21]. A higher LPS level was also associated with greater $CD8^+$ T cell activation.

Clinical outcome

Crowell and Hatano have shown that ECs are at an increased risk of all causes of hospitalisations compared with medically controlled individuals with HIV-1. Some have attributed this to the chronic and low-grade persistent inflammation, which can be harmful overtime [33].

Studies, including those by Okulicz *et al*. and Crowell and Hatano [4,33], evaluated hospitalisation causes among ECs showing a predominance of cardiovascular (CV) and psychiatric disease. Chest pain (26.1%), coronary artery disease (13.0%) and heart failure (13.0%) were the most common diagnoses leading to CV hospitalisation [34]. Studies have shown that individuals living with HIV-1 are more prone to both clinical and subclinical CV diseases [35]. When using coronary computer tomography, Pereyra *et al*. found atherosclerotic plaques to be significantly increased in ECs compared with HIV-1-negative controls, but not in treated non-controllers [35]. They also had significantly higher markers in comparison with HIV-1-negative controls (sCD163, sCD14, hsIL6 and CXCL10), with sCD163 remaining significantly elevated compared with treated non-controllers. In a study by Hsue *et al*. assessing carotid artery intima–media thickness (IMT) in a diverse cohort of HIV seronegative and seropositive adults, ECs showed a trend towards higher median IMT than that in untreated non-controllers [34].

Clinical progression of HIV infection can occur in ECs and AIDS can develop at any point. Moreover, a subset of ECs may suffer from a decrease in $CD4^+$ T cell counts while undetectable. A study by Leon *et al*. showed that ECs with a shorter length of follow-up, hepatitis C co-infection, a sexual risk of HIV-1 infection, a higher VL and a lower nadir $CD4^+$ T cell, were reported to be at a higher risk of virological progression [36]. It was postulated that these individuals suffered a decrease in $CD4^+$ T cells as a result of a reduced thymic output. Most ECs with simultaneous uncompromised thymic function and extrathymic processes with elevated levels of circulating recent thymic emigrants maintain normal total $CD4^+$ T cell levels. The loss of $CD4^+$ T cells, residual HIV replication and basal levels of immune activation seem to influence progression in ECs and should be considered for the management of ECs.

Pernas *et al*. have aimed to identify the factors leading to the loss of natural virological control among ECs [8]. A lower *gag*-specific T cell polyfunctionality, higher viral diversity and levels of proinflammatory cytokines were associated with future loss of virological control. Among different biomarkers, RANTES was found to be the most predictive one with a four-fold increase in transient *vs* persistent ECs.

The role of antiretroviral therapy in elite controllers

Heterogeneity of genetic background, immune responses and clinical outcomes are noted in ECs compared with other HIV-1-positive individuals. A few studies have actually explored the role of ART in these individuals.

Okulicz *et al*. [37] aimed at assessing the role of ART among HIV controllers and compared them with non-controllers on ART. A significant increase in $CD4^+$ T cell count occurred following initiation of ART for all groups ($P<0.001$ for all) but was less dramatic for ECs and was independent of pretherapy VL characteristics, as confirmed by Boufassa *et al*. [38]. After following up a group of ECs and starting only one of those individuals on zidovudine, Sedaghat *et al*. noted a decrease in immune activation in this individual [39]. In addition to the effect of ART on $CD4^+$ T cell count, a study by Chun *et al*. showed that the size of the pool of $CD4^+$ T cells containing infectious HIV-1 decreased significantly after ART initiation and returned to baseline levels upon ART cessation when using tenofovir, emtricitabine and raltegravir for 9 months [40]. These data are supported in a further study by Hatano *et al*. [41]. Ultrasensitive plasma and rectal HIV-1 RNA levels were significantly decreased in controllers after ART initiation in the latter study together with a substantial decrease in markers of T cell activation/dysfunction supporting the concept of persistence of viral replication in untreated ECs contributing to the chronic inflammatory state, even in the absence of detectable viraemia.

Clinical data are still lacking, however, and further studies to assess the efficacy of ART in preventing progression or other non-AIDS-defining comorbidities are needed in ECs but may be difficult to perform because of the small number of such individuals [42,43]. As mentioned in the latest US treatment guidelines, 'Nevertheless, there is a clear theoretical rationale for prescribing ART to HIV controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection' [43].

In addition to ART, other agents possessing anti-inflammatory effects and cardioprotective activity may have a role in the management of ECs. The main clinical concern lies in the chronic inflammatory state and immune activation associated with a risk of CV disease.

Conclusions

The EC phenotype represents a rare, yet complex, subgroup of individuals living with HIV-1. Additional studies are needed to better understand the mechanisms underlying their spontaneous virological control. Their clinical outcomes remain under investigation, but studies suggest that ART should be considered in this group of individuals due to their potential for clinical progression.

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