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MINIREVIEW

Antigen-Dependent and -Independent Mechanisms of T and B Cell Hyperactivation during Chronic HIV-1 Infection▽

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Continuous loss of CD4$^+$ T lymphocytes and systemic immune activation are hallmarks of untreated chronic HIV-1 infection. Chronic immune activation during HIV-1 infection is characterized by increased expression of activation markers on T cells, elevated levels of proinflammatory cytokines, and B cell hyperactivation together with hypergammaglobulinemia. Importantly, hyperactivation of T cells is one of the best predictive markers for progression toward AIDS, and it is closely linked to CD4$^+$ T cell depletion and sustained viral replication. Aberrant activation of T cells is observed mainly for memory CD4$^+$ and CD8$^+$ T cells and is documented, in addition to increased expression of surface activation markers, by increased cell cycling and apoptosis. Notably, the majority of these activated T cells are neither HIV specific nor HIV infected, and the antigen specificities of hyperactivated T cells are largely unknown, as are the exact mechanisms driving their activation. B cells are also severely affected by HIV-1 infection, which is manifested by major changes in B cell subpopulations, B cell hyperactivation, and hypergammaglobulinemia. Similar to those of T cells, the mechanisms underlying this aberrant B cell activation remain largely unknown. In this review, we summarized current knowledge about proposed antigen-dependent and -independent mechanisms leading to lymphocyte hyperactivation in the context of HIV-1 infection.

Chronic immune activation is hallmarked by an overtly activated immune system, which includes aberrant activation of the adaptive immune system comprising T and B cells. T cell activation during chronic HIV-1 infection is closely linked to CD4$^+$ T cell depletion, disease progression, and sustained viral replication (56). This aberrant activation of T cells is observed mainly for memory CD4$^+$ and CD8$^+$ T cells (68) and is documented by increased expression of the surface activation markers CD38 and HLA-DR (133), increased cell cycling, and spontaneous apoptosis (68, 70, 88, 103). Importantly, the majority of these activated T cells are neither HIV specific nor HIV infected (37, 63, 80). The antigen specificities of hyperactivated T cells are largely unknown, as are the mechanisms involved in their activation (4, 56).

B cells are also severely affected by HIV-1 infection, which is manifested in major changes in B cell subpopulations, B cell hyperactivation, and hypergammaglobulinemia (89, 105). B cell hyperactivation and its associated disturbances might be beneficial to the virus as ways to circumvent an efficient antiviral B cell response (69, 105). Similar to those for T cells, the mechanisms underlying this aberrant B cell activation remain largely unknown and are a matter of intense and sometimes controversial research.

In a healthy immune system, the induction of an adaptive immune response relies on the antigen specificity of the T or B cell receptor (TCR or BCR, respectively) and is dependent on the presence of cognate antigen and costimulatory signals. Contrary to some earlier hypotheses, the vast majority of activated T cells during acute viral infections have been shown (in the mouse model) to be antigen specific (107), with limited/absent activation of T cells with unrelated specificities (7). Thus, the impact of antigen-independent T cell activation in healthy individuals is suggested to be negligible, but it might be relevant in pathogenic situations of chronic inflammatory character, such as autoimmune diseases and as discussed here in HIV-1 infection (7). Polyclonal B cell activation independent of BCR specificity, together with hypergammaglobulinemia, is also often described in the context of acute virus infections and autoimmune diseases (75, 105).

The mechanisms underlying aberrant T and B cell activation in HIV-1 infection, as well as the associated antigen specificities, are still debated, and a large body of observations points toward different underlying mechanisms that may even be contradictive. In this review, we discuss possible contributions of antigen-dependent and -independent mechanisms to aberrant T and B cell activation in HIV-1 infection.

HIV-ASSOCIATED T CELL ACTIVATION

One major driving force of HIV-1 disease progression is chronic immune activation. In terms of T cells, this is manifested by increased frequencies of T cells with an activated phenotype (54) and increased turnover of T cells (67, 103). Activation-induced T cell apoptosis or exhaustion and disturbance of T cell homeostasis (70, 88) are the consequences contributing to immunodeficiency. Several studies have shown that T cell activation levels (e.g., the frequency of CD38$^+$ CD8$^+$ T cells) are predictive of disease progression (16, 30, 38, 51, 67, 154). Importantly, hyperactivation of CD4$^+$ T cells

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creates targets for the virus itself to further promote replication, since activated $CD4^+$ T cells are the main source of viral infection and active replication (36, 55).

During primary HIV infection, massive and rapid depletion of $CD4^+$ T cells occurs via direct infection, predominantly in mucosal tissues such as the gastrointestinal tract (GI), and depletion of $CD4^+$ T cells persists into the chronic phase of infection (57, 101, 150). Opposed to these early events mostly related to $CD4^+$ T cell death by HIV infection is the ensuing chronic phase of HIV infection, which is characterized by persistent immune activation leading to a further decline in $CD4^+$ T cells. Throughout the course of chronic HIV infection, only a small fraction of $CD4^+$ T cells is productively infected (3, 39, 63), and the majority of hyperactivated $CD4^+$ T cells are neither HIV specific nor HIV infected (13, 37, 63, 80). Furthermore, apoptosis also occurs in uninfected T cells (29, 43). HIV replication seems to actively drive immune activation, because antiretroviral therapy (ART)-mediated suppression of HIV replication results in the slow normalization of T cell activation (22, 68, 84). However, there are also reports about high levels of immune activation and disease progression in HIV-1 elite controllers, even in the absence of viral replication (74). Thus, HIV-1 replication alone cannot completely account for the extent of T cell hyperactivation.

Since cellular activation and apoptosis pathways share many molecular features (e.g., activation of the caspase pathway and nuclear condensation) (1) and apoptotic cells have been found to express T cell activation markers, it is not surprising that activation and cell death are closely related, e.g., by the process of activation-induced cell death (AICD). Indeed, currently it is thought that activation-induced apoptosis mechanisms act as a major link between systemic immune activation and $CD4^+$ T cell depletion (36, 43, 54), which are the two hallmarks of HIV-1 infection.

Recently, another mechanism that contributes to immune activation-induced depletion of naïve T cells in HIV or simian immunodeficiency virus (SIV) infection has been described: sustained immune activation leading to fibrosis in lymphoid tissues, limiting access of T cells to their survival factor, interleukin-7 (IL-7), which is produced predominantly by fibroblastic reticular cells. As fibroblastic reticular cells depend for their survival on lymphotoxin-β (produced by T cells), they are depleted with progressive infection and hence no longer provide the IL-7 critical for T cell survival (156).

In this section of the review, we discuss different mechanisms contributing to the uncontrolled hyperactivation (and apoptosis associated therewith) of non-HIV-specific T cells during chronic HIV-1 infection which is associated with exhaustion and immune dysfunction. In this context, we discuss (i) antigen-dependent and (ii) antigen-independent T cell activation mechanisms promoted by HIV infection. Furthermore, we also discuss (iii) homeostatic proliferation of T cells in response to HIV-induced lymphopenia as a potential mechanism of T cell hyperactivation.

(i) Costimulation of antigen-dependent T cell activation. Chronic HIV-1 infection is associated with elevated levels of proinflammatory cytokines and virus- or bacteria-derived Toll-like receptor (TLR) ligands and modulation of antigen-presenting cells (APCs). All these factors may be relevant for costimulation of non-HIV-specific T cells (Fig. 1A; Table 1) in the context of the presence of low levels of non-HIV antigens. In the context of suboptimal TCR stimulation, which occurs if the level of TCR stimulation is insufficient to induce T cell activation in the absence of a costimulatory signal, provision of appropriate costimulation in the form of an inflammatory milieu in combination with APCs might facilitate activation of non-HIV-specific T cells.

Before we discuss possible mechanisms involved in antigen-dependent stimulation of non-HIV-specific T cells during chronic HIV infection, we would like to introduce several possible sources of antigenic stimulation which have been discussed previously in the context of HIV-1 pathogenesis (4, 56). It should be noted, however, that in many cases direct *in vivo* or even experimental *in vitro* evidence needed to assess their actual contribution is missing. However, it is clear that HIV infection occurs in hosts that harbor multiple other (often persistent) microbes whose immune control might be compromised in the setting of HIV-induced immunodeficiency. In particular, coinfecting viruses such as hepatitis C virus (HCV), herpes simplex virus 2 (HSV-2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human T cell leukemia virus type 2 (HTLV-2) have been shown to contribute to HIV pathogenesis and possibly to chronic lymphocyte activation. The HIV-induced disturbance of an established equilibrium between persistent microbes, viruses in particular, and host immune control with respect to the impact on HIV pathogenesis is excellently reviewed in reference 93.

Possible sources of non-HIV-related antigenic stimulation in chronic HIV-1 infection. In 2006, Brenchley and colleagues introduced the concept of microbial translocation as a potential source of chronic immune activation (19, 20, 109). Massive depletion of $CD4^+$ T cells in the mucosal lymphoid tissue leads to increased gut permeability, allowing for systemic translocation of microbial products (e.g., lipopolysaccharide [LPS], flagellin, and CpG) and gut mucosal antigens from the gut. This is discussed as a source of antigenic stimulation in HIV-1 pathogenesis in references 7 and 56. Furthermore, recent work has established that a profound loss of IL-17-producing $CD4^+$ T cells in circulation and mucosal tissues in HIV-infected individuals leads to a concomitant increase of immunosuppressive regulatory T cells (Tregs) (41). This change in Th17-Treg balance was associated with the induction of indoleamine 2,3-dioxygenase 1 (IDO) by myeloid DCs and might further contribute to the loss of mucosal integrity and thereby to chronic inflammation driven by gut microbial products.

HIV-associated immunodeficiency results in suboptimal immune control of persistent herpesviruses such as CMV and EBV (93). Their reactivation and replication could provide a source of antigenic stimulation in HIV-1 infection (4, 56). Data from our laboratory and others have provided direct experimental evidence for a role of persistent herpesvirus antigens in driving activation of $CD4^+$ T cells with herpesvirus specificities during active HIV-1 replication, even in the absence of measurable reactivation of persistent herpesviruses (34, 38, 59, 115, 152).

Autoantigens may also provide a pool of antigenic stimulation in HIV-1 infection (56). Indeed, induction of self-reactivate $CD8^+$ T cells in the context of HIV infection has been described (123).

HIV-1 infection may provide costimulation to suboptimally

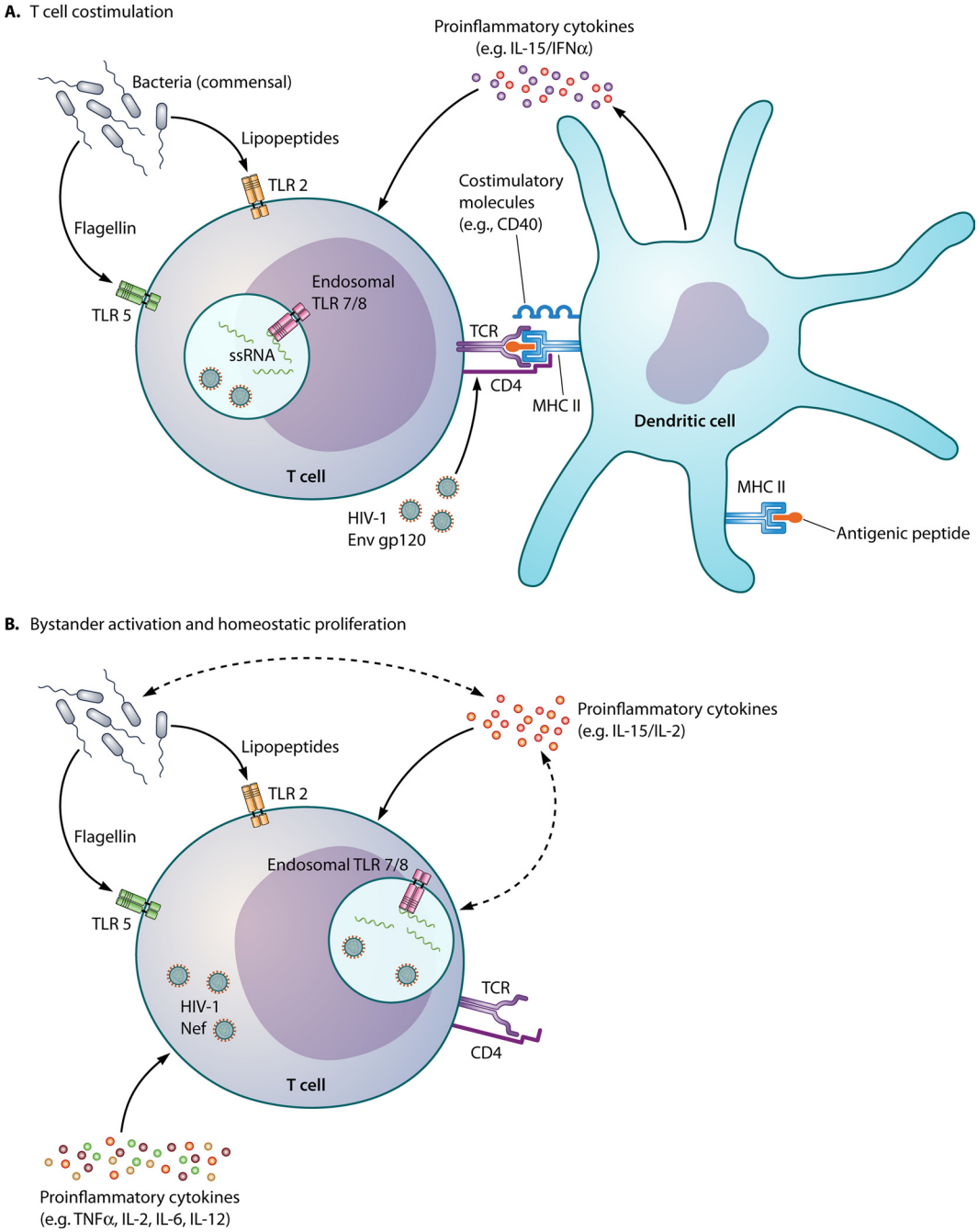

FIG. 1. Potential mechanisms contributing to aberrant T cell activation in HIV-1 infection. (A) Costimulation resulting in enhanced antigen-dependent ($CD4^+$) T cell activation can be mediated by interaction of HIV-1 envelope glycoprotein gp120 with the CD4 coreceptor or by stimulation of TLR2, -5, or -7/8 via bacterial lipopeptides, flagellin, and HIV-1-derived ssRNA, respectively, or by proinflammatory cytokines such as IL-15 and IFN-α and/or costimulatory molecules expressed by (partially) activated dendritic cells. (B) In the absence of TCR stimulation, bystander activation of T cells may be induced by intracellular expression of HIV-1 Nef protein or by synergizing effects of TLR stimulation by IL-15 or IL-2 and/or different combinations of proinflammatory cytokines such as IL-2, IL-6, TNF-α, IL-12, or IL-15. Furthermore, lymphopenia-driven and cytokine-mediated homeostatic proliferation leads to acquisition of activation phenotypes in T cells. Only the mechanisms that most likely directly act on ($CD4^+$) T cells are depicted.

TCR-stimulated T cells via the following not mutually exclusive mechanisms (Fig. 1; Table 1): (i) HIV-1 proteins or HIV-1/bacteria-derived TLR ligands, (ii) proinflammatory cytokines, or (iii) activation of APCs.

Costimulation by HIV-1 proteins and TLR ligands. The HIV-1 envelope glycoprotein gp120 has been shown to costimulate activation of $CD4^+$ T cells if provided simultaneously with suboptimal TCR stimulation (113; also unpublished ob-

TABLE 1. Triggers of antigen-dependent and -independent T cell activation

Activation stimulus	Cell type	Read out for activation	Reference(s)
Costimulation of antigen-dependent activation			
HIV-1 proteins and TLR ligands			
HIV-1 gp120 + anti-CD3	Human naïve and memory $CD4^+$ T cells	Proliferation and IL-2 production	113
HIV-1 Nef + anti-CD3	Human PBMCs	Proliferation and cytokine production via IL-15 induction in monocytes	119
TLR2 ligand + anti-CD3 + IFN-α	Human naïve and memory $CD4^+$ T cells	Proliferation and cytokine production (for memory more potent than that for naïve $CD4^+$ T cells)	86
TLR2 ligand + anti-CD3 or antigen	Naïve mouse $CD8^+$ T cells	Proliferation, survival, and effector functions	28
TLR5 or TLR7/8 ligand + anti-CD3	Human naïve and memory $CD4^+$ T cells	Proliferation and cytokine production	23
TLR9 ligand + anti-CD3	Naïve mouse $CD4^+$ and $CD8^+$ T cells	Proliferation; CD25 expression; cytokine production; cytotoxicity	9
TLR4 ligand + antigen	Mouse $CD4^+$ and $CD8^+$ T cells	Proliferation	135
Proinflammatory cytokines			
IL-15 + antigen	Human PBMCs	Proliferation	116
IL-15 + antigen	Human $CD8^+$ T cells	Proliferation and cytotoxicity	81
Type I interferon + anti-TCR	Mouse T cells	Inhibition of proliferation; expression of activation marker CD69	135, 140
Type I interferon + APCs	Mouse $CD8^+$ T cells	Proliferation (possibly via type I interferon-induced release of IL-15)	135, 140
Type I interferon	Human $CD4^+$ T cells	Downregulation of BTLA, associated with increased upregulation of activation markers and cytokine production after anti-CD3 stimulation + anti-BTLA cross-linking	157
Activation of dendritic cells			
LPS or inactivated HIV + suboptimal antigen concn	Human memory $CD4^+$ T cells	Proliferation	59
TLR ligands + antigen	Human memory $CD4^+$ and $CD8^+$ T cells	Cytokine production	95
Inactivated HIV	Human PBMCs	Proliferation (alloresponse)	62
HIV (via IFN-α production by pDCs)	Human PBMCs	Reduced proliferation after TCR stimulation via DC-expressed IDO	15
Antigen-independent activation			
HIV-1 proteins and TLR ligands			
HIV-1 Nef ± anti-CD2	Human PBMCs	Proliferation via IL-15 induction in monocytes	119
HIV-1 Nef	Jurkat T cell line	Transcription profile	131
TLR2 ligand + IL-2 or IL-15	Human memory $CD4^+$ T cells	Proliferation; cytokine production	86
TLR2 ligand + IL-7 or IL-2	Memory mouse $CD8^+$ T cells	Proliferation; IFN-γ secretion	27
TLR5 or TLR7/8 ligand + anti-CD2 or IL-2	Human naïve and memory $CD4^+$ T cells	Proliferation; cytokine production	23
TLR2, -3, -4, -5, -7, -8, -9 ligands	Human PBMCs	For $CD8^+$ T cells, activation marker (CD38, CD69); for $CD4^+$ T cells, CD38 expression and entry into cell cycle with ensuing cell death	49
Proinflammatory cytokines			
IL-2, IL-6, and TNF-α	Human naïve and memory $CD4^+$ T cells	Proliferation (naïve and memory cells); cytokine production and B cell help (memory cells)	149
IL-2	Human PBMCs	Proliferation	116
IL-15 or IL-2 in CD4-monocyte cocultures	Human $CD4^+$ T cells	IFN-γ production	5
IL-15 + IL-12	Human $CD4^+$ T cells	IFN-γ production	5
IL-15	Human $CD4^+$ T cells	Proliferation	5
IL-15	Human Memory $CD8^+$ T cells	Transcription profile; proliferation; cytokine production; cytotoxicity	93
Type I interferon (*in vivo*)	Mouse $CD8^+$ T cells ($CD44^+$)	*In vivo* proliferation (likely mediated by IL-15); CD69 upregulation	135, 147, 148
Type I interferon	Human PBMCs	Inhibition of spontaneous apoptosis; CD38 upregulation on $CD8^+$ T cells	125
Type I interferon	Human PBMCs	CD38 and CD69 upregulation on $CD4^+$ and $CD8^+$ T cells	15
Supernatants from PBMCs after T cell activation	Human memory $CD4^+$ T cells	CD25 and CD69 expression; transcription profile	6
Homeostasis-induced activation			
Lymphopenia	Naïve $CD4^+$ and $CD8^+$ T cells	Homeostatic proliferation; expression of CD69 and CD25; acquisition of memory phenotype	6, 50, 52, 58, 61, 77, 112, 144

servation from our laboratory). This activation is based on the interaction of HIV-1 gp120 with the CD4 coreceptor, which might facilitate phosphorylation events involved in early TCR signaling (92).

The HIV-1 accessory protein Nef was shown to increase the proliferative response to suboptimal TCR stimulation when added exogenously to peripheral blood mononuclear cell (PBMC) cultures (119). However, this costimulation is possibly indirect, via the induction of proinflammatory cytokines in accessory cells.

Chronic HIV-1 infection is associated with an increased abundance of TLR ligands (e.g., due to the microbial translocation

described above). These microbial TLR ligands comprise bacterial products such as lipopeptide (TLR2/1 or TLR2/6 ligand), LPS (TLR4 ligand), flagellin (TLR5 ligand), and bacterial DNA containing CpG motifs (TLR9 ligands). Furthermore, HIV-inherent components such as single-stranded RNA (ssRNA) are ligands for TLR7 in mice and TLR8 in humans (72). Several TLRs are known to be expressed by human T cells, and the expression of at least some of them is regulated by TCR-dependent cellular activation (79). TLR signaling might modulate T cell responses in the presence of suboptimal TCR stimulation in a costimulatory manner. Memory $CD4^+$ T cells constitutively express TLR2, which recognizes bacterial lipopeptide, and TLR2 stimulation has indeed been shown to provide T cell costimulation (86). Furthermore, it was shown that TLR2 acts as a costimulatory receptor on TCR-stimulated, highly purified murine $CD8^+$ T cells (28). Another study showed that signaling of TLR5 via flagellin or TLR7/8 via ssRNA also enhances $CD4^+$ T cell activation in response to suboptimal TCR stimulation (23). TLR9 costimulation was shown to enhance proliferation of murine $CD4^+$ T cells (9). Interestingly, $CD4^+$ T cells express TLR4 but are unable to respond to its ligand, LPS (86). This suggests that increased levels of plasma LPS cannot directly translate into increased $CD4^+$ T cell activation.

Costimulation by proinflammatory cytokines. Increased levels of many proinflammatory cytokines, such as IL-1, IL-2, IL-6, IL-10, IL-15, IL-18, alpha interferon (IFN-α), IFN-γ, and tumor necrosis factor alpha (TNF-α) have been reported during HIV-1 infection (4, 14, 137). IL-15 and IFN-α have specifically been described in the context of human T cell costimulation.

IL-15 was shown to generally enhance antigen-induced proliferation of PBMCs from HIV-1-seropositive individuals (116). This was confirmed separately for HIV-specific $CD8^+$ T cells (81). Monocytes as a possible source of IL-15 during HIV-1 infection are discussed in reference 119.

Plasmacytoid dendritic cells (pDCs) are probably the main source of IFN-α in HIV-1 infection (44). Type I interferons were shown to differentially impact antigen-induced T cell activation, depending on the absence or presence of APCs. In an APC-free *in vitro* system, type I interferon inhibits T cell proliferation and has no impact on cytokine production, while leading to the upregulation of early T cell activation markers such as CD69. However, it promotes T cell proliferation when induced by viable APCs. It is conceivable that type I interferons negatively regulate cell cycle entry in the absence of APCs. However, in the presence of APCs and antigen, the APC-maturing properties of type I interferons dominate and enhance antigen-induced proliferation (140).

Furthermore, IFN-α was shown to downregulate the B and T lymphocyte attenuator (BTLA) protein on $CD4^+$ T cells, which resulted in heightened responsiveness to polyclonal stimulation in the presence of agonistic BTLA antibodies (157).

Costimulation by dendritic cells. During chronic HIV-1 infection, DCs are frequently reported to acquire a partially activated phenotype which is reflected by moderate upregulation of CD40/CD86 as well as by spontaneous production of proinflammatory cytokines/chemokines (2, 8, 33). Partial activation of dendritic cells (DCs) might occur in the presence of proinflammatory cytokines and TLR ligands, which are abundant due to the microbial translocation (20, 32, 109). We have recently provided evidence that this partial activation of DCs contributes to increased activation of persistent herpesvirus-specific $CD4^+$ T cells during chronic HIV-1 infection (59). In line with this finding, our *in vitro* experiments provide evidence that *in vitro* HIV-activated monocyte-derived dendritic cells (MDDCs) are superior to unstimulated MDDCs in antigen presentation to CMV-specific memory $CD4^+$ T cells (59). Furthermore, it has been shown that TLR-stimulated DCs augment memory responses of HIV- and CMV-specific T cells (95), and HIV-stimulated DCs show increased stimulatory capacity for allogeneic T cells (62).

(ii) TCR-independent activation of T cells. In addition to the antigen-dependent costimulation of T cells as discussed above, antigen-independent activation may contribute to aberrant T cell activation in the context of HIV-1 infection (7) (Fig. 1B; Table 1). In this context, TCR-independent T cell activation is defined as the induction of phenotypic or functional changes that characterize activated T cells via a mechanism that is independent of specific TCR stimulation. Since immune responses are often associated with extensively proliferating T cells and precursor frequencies of T cells for specific antigens are low, it is conceivable that a proportion of proliferating T cells might be activated in a TCR-independent manner, at least during early time points of infection when antigen-specific T cells have not yet clonally expanded to their peak (146). Indeed, one study suggests that activated T cells in HIV-1 infection, albeit primarily of a memory phenotype, rarely show signs of recent TCR stimulation (130). However, this conclusion was based on the analysis of cell surface expression of CD69 and CD25, which are known to be very transiently expressed after TCR stimulation and hence might not provide direct evidence of whether or not cognate antigen stimulation is involved in the accumulation of activated T cells (as defined by CD38 and HLA-DR expression) during HIV infection (6, 149).

There is much evidence that TCR-independent T cell activation involves cytokine stimulation or cross-linking of certain membrane-bound receptors by viral and microbial components. In contrast to a classical T cell response to infection, TCR-independent T cell activation obviates the need for specific TCR stimulation and thereby bypasses certain TCR-dependent control checkpoints (6). So far, the relevance of TCR-independent T cell activation in chronic HIV infection (compared with that in healthy individuals) is not known, but it is likely that the inflammatory milieu present during untreated HIV infection has a substantial impact on the induction of T cell hyperactivation and thereby contributes to disease progression.

TCR-independent T cell activation by HIV-1 proteins and TLR ligands. The previously mentioned HIV accessory protein Nef was shown not only to enhance suboptimal TCR triggering but also to synergize with suboptimal costimulatory anti-CD2 stimulation (119). In addition, Nef expression in Jurkat T cell lines was shown to induce a transcriptional profile that is 97% identical to that of anti-CD3 stimulation (131). However, cellular expression of Nef would most likely be restricted to cells directly infected with HIV *in vivo* and thus is unlikely to account for the activation status of the vast majority of noninfected- but activated- T cells *in vivo*.

Memory T cells are directly responsive to TLR2 stimulation

in the absence of cognate antigen and especially in the concomitant presence of the proinflammatory cytokines IL-2 and IL-15 (27, 86) Similarly, TLR5 and TLR7/8 have been shown to enhance T cell activation in the absence of TCR stimulation but also to require the presence of other stimuli such as IL-2 and anti-CD2 stimulation (23).

Finally, cultivation of purified T cells with a number of TLR ligands induces expression of CD69 on $CD8^+$ T cells and cell cycle entry of $CD4^+$ T cells (49).

TCR-independent T cell activation by proinflammatory cytokines. Several cytokines might be relevant to antigen-independent activation of human $CD4^+$ T cells. A combination of IL-2, IL-6, and TNF-α was shown to activate purified naïve and resting memory $CD4^+$ T cells (149). Abundant data documenting the capability of IL-15 to mediate TCR-independent activation of T cells are available; however, there are conflicting results with respect to the requirement of additional stimuli. One study reported that IL-15 failed to induce TCR-independent T cell proliferation, while IL-2 was able to potently induce antigen-independent lymphocyte proliferation (116). The addition of IL-15 to cocultures of T cells and monocytes stimulated $CD4^+$ cells but not $CD8^+$ T cells, and this stimulation involved IL-12 as well as CD40/CD40L interaction (5). T cell activation induced by the exogenous addition of Nef, as described above, possibly involves stimulation of monocytes/macrophages and the subsequent secretion of IL-15 (119). Similar to Nef, IL-15 has been reported to induce a transcriptional profile resembling anti-TCR stimulation in $CD8^+$ T cells (94).

Mouse memory $CD8^+$ T cells (CD44hi) undergo TCR-independent proliferation when exposed to type I interferons *in vivo*, and the action of type I interferons on T cells might be mediated by IL-15 (135, 148). In line with this finding, another study suggested that pDC-derived IFN-α downregulates the BTLA protein during chronic HIV-1 infection, which is associated with T cell hyperactivation in a TCR-independent manner (157). Injection of LPS into mice showed proliferation of memory $CD8^+$ T cells via an indirect pathway involving LPS stimulation and the release of type I interferon (147). Further evidence for a contributing role of type I interferon in T cell hyperactivation comes from studies of SIV-infected macaques, in which sustained induction of interferon-stimulated genes correlated with lymphocyte hyperactivation and disease progression which is absent in SIV-infected natural hosts such as sooty mangabeys (17, 76). Furthermore, exposure of T cells to type I interferon in the absence of TCR triggering leads to upregulation of the T cell activation markers CD38 and CD69 (15, 125).

An elegant *in vitro* study reassessed the induction of TCR-independent T cell activation in cocultures with $CD4^+$ T cells which were activated in a TCR-dependent manner, demonstrating that human memory $CD4^+$ T cells are most susceptible to TCR-independent activation (6). This finding resonates with memory $CD4^+$ T cells also being the subpopulation of T cells which is mainly affected by aberrant immune activation during HIV-1 infection *in vivo* (66). The reported TCR-independent activation was shown to rely solely on soluble factors secreted by the pool of TCR-stimulated PBMCs and did not require cell-to-cell contact. Unfortunately, the study did not more closely identify the nature of these soluble factors (6).

(iii) Homeostasis-induced T cell activation. T cell homeostasis is a physiological process to maintain constant levels of T cells by balancing death, survival, and proliferation throughout life. Generation of T lymphocytes is adjusted by the combination of thymic-dependent (thymopoiesis) and thymic-independent (homeostatic proliferation of existing cells) pathways (78, 134, 141). IL-7 and IL-15 are critical cytokines involved in T cell homeostasis to regulate peripheral T cell levels. Constitutive production of low levels of these cytokines is critical for T cell survival, whereas increased levels promote homeostatic proliferation. This homeostatic response results in a T cell population that is composed primarily of memory and effector T cells with a polyclonal TCR repertoire comparable to that of the naïve population (48).

Peripheral homeostatic proliferation takes place in lymphopenic situations such as that induced by the substantial loss of $CD4^+$ T cells in the context of HIV-1 infection (70). Increased turnover rates of both $CD4^+$ and $CD8^+$ T cell subsets in blood and lymph nodes (45, 70, 71, 102, 103, 126), as well as in organs (132), have consistently been described. In line with the increased turnover of these cells, it was shown that levels of the homeostatic cytokine IL-7 negatively correlate with $CD4^+$ T cell counts and disease progression (108). Homeostatic proliferation of naïve T cells converts them to a memory phenotype (52, 58, 77, 112, 144) and generates upregulation of activation markers CD69 and/or CD25 (50, 61). Therefore, HIV-1-induced homeostatic proliferation of naïve T cells might contribute to T cell hyperactivation.

However, some studies suggest that the increased turnover of T cells during chronic HIV-1 infection is not driven by $CD4^+$ T cell depletion alone, but rather is caused by HIV-1-associated immune activation (68, 70, 88, 103). This view is supported mainly by the fact that other nondepleted circulating lymphocytes (e.g., $CD8^+$ T cells) are also recruited into cycles of activation and proliferation during HIV infection (53). Furthermore, successful control of HIV replication by ART results in an immediate decline in proliferating T cells, despite often very low $CD4^+$ T cell numbers, lending further support to the notion that increased T cell proliferation during untreated HIV infection is not solely a homeostatic response (68). Furthermore, plasma HIV levels were shown to be a primary determinant of memory and naïve $CD8^+$ T cell turnover, also pointing to increased T cell turnover as a direct consequence of HIV infection rather than as simply a homeostatic response to CD4 T cell depletion. However, for naïve $CD4^+$ T cells, the major driving force of turnover seems to be $CD4^+$ T cell depletion (136). A recent observational study suggested that both the inflammatory response to HIV infection and the homeostatic response to $CD4^+$ T cell depletion contribute to increased proliferation of naïve $CD4^+$ T cells, whereas naïve $CD8^+$ T cell proliferation was driven mainly by levels of HIV (24, 25). *In vivo* cell cycle analysis using bromodeoxyuridine incorporation showed that activated $CD4^+$ and $CD8^+$ T cells exhibited higher proliferation rates than memory cells, while naïve cells showed the lowest turnover rates. This finding indicates that HIV represents the main source of cellular activation and proliferation for subsets of both $CD4^+$ and $CD8^+$ T cells, with the exception of naïve $CD4^+$ cells, whose proliferation is most likely a homeostatic response to lymphopenia (136).

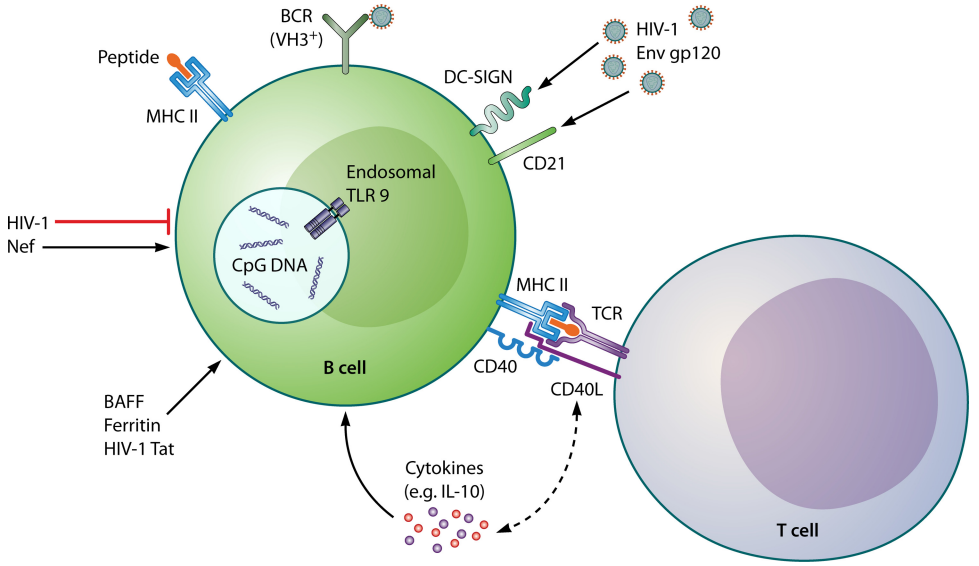

FIG. 2. Mechanisms potentially contributing to polyclonal B cell activation in HIV-1 infection. Polyclonal B cell activation independent of BCR stimulation can be induced by interaction of the HIV-1 envelope glycoprotein gp120 with the coreceptors DC-SIGN and CD21 or with VH3$^+$ BCRs, by TLR9 stimulation via bacterial or virus-derived CpG DNA, and/or by T cell-mediated CD40/CD40L interaction in combination with cytokines (including IL-10, IL-2, IL-3, and IL-4) and exposure to increased levels of BAFF and ferritin. HIV-1 Nef and Tat were also shown to promote B cell activation with contradicting results for Nef, which was also reported to inhibit class switch recombination in B cells. Only the mechanisms that are most likely to act directly on B cells are depicted.

The connection between CD4$^+$ T cell depletion and increased levels of proliferating (and going along with this, activated) T cells is complex and may not be explained simply by either lymphopenia-induced homeostatic proliferation or by HIV-1-associated immune activation alone but rather by an interplay of both and even perhaps by additional factors.

HIV-ASSOCIATED B CELL ACTIVATION

HIV infection is associated with severe B cell disturbances (105), and memory B cell responses are reported to be impaired, particularly in the context of vaccinations (31, 64, 97, 111, 117). Hyperactivation of B cells during untreated chronic HIV-1 infection is also part of these disturbances and is characterized mainly by increased expression of surface activation markers, increased polyclonal B cell activation, increased cell turnover, increased frequencies of plasmablasts, and manifestation of hypergammaglobulinemia (31, 88, 89, 105, 111, 129). The extent of HIV-associated hypergammaglobulinemia and B cell activation is not exclusively linked to HIV specificity, as less than 20% of Ig-secreting B cells have been shown to be specific for gp160 and less than 10% specific for p24 (129). B cell hyperactivation and hypergammaglobulinemia of nonpathogen specificity are frequently observed upon many viral and bacterial infections and in the context of autoimmune diseases (105). A role for an antigen-dependent mechanism underlying B cell hyperactivation during HIV-1 infection could so far not be completely excluded. Indeed, elevated levels of autoantibodies (including specificities for DNA, lipids, actin, and myosin) are commonly found in HIV-infected individuals (65, 110, 129), but polyreactive B cells with irrelevant specificities (e.g., for ovalbumin or haptens) are also found (129). However, the vast majority of published reports indicates that polyclonal stimulation independent of BCR specificity may lead to B cell hyperactivation and hypergammaglobulinemia (31, 75, 105) (Fig. 2; Table 2).

BCR-dependent polyclonal B cell activation with non-HIV specificity. HIV-1 infection and pathogenesis are tightly linked to the infection of the GI tract (19, 101), as intestinal CD4$^+$ T cells are preferential targets of the virus and are massively depleted early during infection (21, 56, 101). HIV enteropathy is well described (87) and is associated with GI tract inflammation (100), malabsorption (87), diarrhea (153), increased intestinal permeability (83, 128), and translocation of microbial products (19, 20, 138). Since microbial translocation from the GI tract is systemic (at least in SIV-infected macaques [40]) and has been closely linked to chronic T cell activation in HIV infection, it is conceivable that it also impacts systemic B cell hyperactivation, perhaps even in an antigen-dependent manner. Indeed, HIV-associated B cell disturbances have been observed not only systemically but also locally in the HIV-infected gut, evidenced by intestinal B cell hyperactivity, destruction of gastrointestinal germinal centers, and intrafollicular impairment of the immunoglobulin switch enzyme activation-induced deaminase (AID) (91, 111, 155). Whether HIV-associated enteropathy and increased systemic exposure to GI tract microbial antigens contribute to HIV-associated hypergammaglobulinemia in an antigen-dependent manner was recently addressed (60). In that study, systemic antibody responses to a selection of GI tract commensals in patients with early or advanced HIV infection were assessed, as were those in patients suffering from inflammatory bowel disease (IBD). Although systemic antibody responses to gut commensal bacteria were abundant in both patient cohorts and in healthy control individuals, there were markedly increased antibody responses against several gut commensal bacteria in IBD patients. How-

TABLE 2. Triggers of antigen-dependent and -independent B cell activation

Activation stimulus	Cell type or response	Read out for activation	Reference(s)
Antigen-dependent activation			
Commensal bacteria	Systemic antibody response	Comparable levels in healthy individuals and HIV patients	60
CMV		Comparable levels in healthy individuals and HIV patients	46, 60, 120
Antigen-independent polyclonal B cell activation			
Viral proteins and TLR ligands			
HIV-1 gp120	Human B cells	Interaction with CD21 and DC-SIGN leads to increased IgG secretion and class switch recombination	69, 104, 124
HIV-1 gp120	Human B cells	Binding to VH3 activates Ig secretion	10
HIV-1 Nef + T cells + IL-6	Human B cells	Plasma cell differentiation	26
HIV-1 Nef	Intrafollicular human B cells	Inhibition of class switch recombination	118, 155
HIV-1 Tat	Human PBMCs	Fas expression on B cells	73
HIV-1 Tat + anti-CD40 + IL-4	Human germinal-center B cells	Proliferation	90
HIV-1 Tat + anti-BCR	Human naïve and memory B cells	Inhibition of proliferation	90
TLR9 ligand	Human memory B cells	Proliferation; Ig secretion	11, 12
Cytokines and T cell help			
CD40 cross-linking + IL-4	Human memory B cells	Plasma cell differentiation	42
CD40 cross-linking + IL-4 + IL-1 + IL-10 + IL-3	Human memory B cells	Ig secretion	85
CD40 cross-linking ± IL-10	Human naïve and memory B cells	Proliferation and plasma cell differentiation of memory B cells	145
Activated $CD4^+$ T cell clones	Human memory B cells	Proliferation; Ig secretion	12
Anti-CD40	Human naïve B cells	Induction of class switch recombination; secretion of IgM and IgG	42
Anti-CD40 + IL-10	Human naïve B cells	Switch factor for IgG1 and IgG3; promotion of plasma cell differentiation	99
Ferritin	Human B cells	Proliferation; Ig production	142
IL-6 + cell adhesion + CD27/CD80 costimulation	Activated human B cells	Ig secretion; plasma cell differentiation	47

ever, in HIV patients, antibody responses to commensal gut bacteria were not altered and were also well maintained in the late stage of disease at levels comparable to those in healthy controls. Even episodes of diarrhea in HIV-infected individuals, being associated with enhanced intestinal permeability (83), had no impact on systemic antibody responses. This suggests that neither the HIV infection-associated immunodeficiency nor the nature of the HIV-induced enteropathy allows excessive B cell activation with specificity for the intestinal microbiota. Therefore, translocating microbiota is unlikely to contribute to hypergammaglobulinemia in an antigen-specific manner.

In the case of T cell responses, there is evidence that T cells with specificity for persistent/latent coinfecting viruses such as CMV and EBV are increased in HIV-infected individuals (4, 34, 59). It is therefore conceivable that antibody responses with specificity for persistent/latent coinfecting viruses might contribute to hypergammaglobulinemia in HIV-1 infection. Indeed, despite the fact that antibody responses to novel antigens and booster vaccines such as tetanus toxoid are impaired during chronic HIV-1 infection (60, 64, 98, 104, 105, 117), CMV IgG levels are equally high or even higher in HIV-infected individuals than in healthy donors in the absence of overt CMV reactivation (46, 60, 120). However, these variable increases in CMV-specific IgG titers in HIV-infected individuals cannot account for the extent of hypergammaglobulinemia observed in these patients, lending further support to a strong component of antigen-unspecific hyperactivation of B cells during untreated HIV-1 infection.

Polyclonal B cell activation by viral proteins and TLR ligands. The HIV-1 envelope glycoprotein gp120 can interact with the complement receptor CD21 and the C-type lectin receptor DC-SIGN, which are both expressed on B cells (104, 122). These interactions have been associated with polyclonal B cell activation, increased spontaneous Ig secretion, and Ig class switching (69, 104, 124). However, the relatively low frequencies of B cells interacting with HIV virions *in vivo* suggest that this might represent only a minor mechanism accounting for the extent of B cell hyperactivation observed in HIV-infected patients (104). Furthermore, HIV-1 gp120 was shown to directly bind and activate Ig secretion of B cells expressing the VH3 gene element in their BCRs in a B cell superantigen-specific manner (10). Again, this B cell super-antigenic property of HIV-1 gp120 is unlikely to account for the sustained B cell activation and hypergammaglobulinemia, as $VH3^+$ B cells were shown to be selectively depleted during HIV-1 infection (82).

Similar to that for T cells, an indirect activatory effect on B cells via HIV-infected macrophages has been ascribed to Nef via secretion of proinflammatory cytokines (143), and recombinant Nef protein was shown to induce plasma cell differentiation *in vitro* in the presence of T cells and mono-

cyte-induced IL-6 secretion (26), but this contradicts reports of direct Nef-induced class switch inhibition in intrafollicular B cells (118, 155).

Furthermore, the HIV accessory protein Tat was also shown to induce B cell activation, as measured by induction of Fas expression upon *in vitro* culture of PBMCs in the presence of recombinant Tat protein (73), and Tat was reported to enhance germinal center B cell proliferation in response to CD40 cross-linking in the presence of IL-4 but inhibited BCR-triggered proliferation of naïve or memory B cells (90).

A role of TLR stimulation in B cells is often discussed in the context of serological maintenance (11, 12) but may well be applicable to hyperactivation and hypergammaglobulinemia. Constitutive TLR expression (TLRs 2, 6, 7, 9, and 10 but not TLR4) in human B cells is confined to the memory compartment (11, 18), indicating that direct TLR signaling on B cells is restricted to memory B cells. Thus, memory B cells respond to TLR9, which recognizes CpG DNA, and start to proliferate and secrete Ig independently of BCR triggering (11, 12). Naïve B cells, however, are reported to upregulate TLR9 only upon activation by BCR triggering (11, 12, 127), which may be relevant in the context of a proposed mechanism, that polyclonally activated naïve B cells are the main contributors to hypergammaglobulinemia (31). It has indeed been shown that B cells from HIV-1-infected donors, despite B cell deficiencies, are responsive to stimulation by CpG DNA (96). The latter may be available in HIV-1 infection either in the form of retrotranscripts of viral genomes, which are found, e.g., within cell-free virions (35), or by bacterial components that may derive from microbial translocation, as discussed previously (19). Increased levels of LPS, however, may be excluded as a direct contributor to polyclonal B cell activation since B cells do not express TLR4 (11, 151).

Polyclonal B cell activation by cytokines and involvement of T cell help. Non-antigen-specific T cell help provided to B cells mainly by CD40-CD40L interaction and cytokines (including IL-2, IL-3, IL-4, and IL-10) can induce B cell activation and plasma cell differentiation, in particular of memory B cells, also in the absence of BCR triggering (12, 85, 145). It has been reported that the frequency of T cells expressing CD40L and thus able to provide costimulation to B cells is increased in HIV-infected individuals (106).

Similar to TLR 9 stimulation, T cell help provided by activated $CD4^+$ T cell clones was shown to induce proliferation and Ig secretion by memory B cells (12). Another study confirmed that CD40 stimulation of memory B cells indeed results in Ig secretion and cell differentiation but is also associated with the induction of apoptosis (42). Interestingly, the same study also showed that prolonged CD40 stimulation of naïve B cells triggered them to class switch and secrete IgG and IgM antibodies (42). Thus, in such a scenario, the *in vivo*-observed hypergammaglobulinemia would be a secondary effect of the high level of activation of $CD4^+$ T cells.

But how are B and T cells in the absence of cognate antigen supposed to interact? A study of murine lymphocytic choriomeningitis virus (LCMV) infection, which is also associated with hypergammaglobulinemia, suggests that B cells can present viral antigen to T cells on major histocompatibility complex class II (MHC-II) molecules independently of their BCR specificity, in particular in the presence of high antigen levels. This TCR-MHC-II interaction then allows spatial proximity between T and B cells to provide CD40-CD40L interaction, which subsequently induces polyclonal B cell activation and hypergammaglobulinemia (75).

CD40L in combination with IL-10 has been directly implicated to be relevant for HIV-1-associated hypergammaglobulinemia (106). Serum levels of IL-10 and CD40L expression on T cells positively correlated with serum Ig levels, and intravenous Ig infusion further increased IL-10 levels. Such positive feedback of increased Ig levels on IL-10 production might be a basis for a vicious cycle in which elevated serum Ig augments IL-10 production and vice versa. IL-10 is important in the regulation of B cell activation and Ig secretion, since it acts as switch factor for IgG production during B lymphocyte maturation and plasma cell differentiation (99, 106).

B cell hyperplasia has been observed both in germinal centers and in extrafollicular areas (114, 121), and it is suggested that particularly extrafollicular CD40-independent polyclonal B cell hyperactivation might be driven by the increased levels of macrophage-derived ferritin and B cell activating factor (BAFF) found in HIV-infected individuals (139, 142).

Finally, another study suggests that IL-6 in combination with adhesion and CD27/CD80 costimulation provided by monocytes and natural killer (NK) cells may contribute to spontaneous Ig secretion and terminal plasma cell differentiation during HIV-1 infection (47).

CONCLUSION

Despite extensive research, the relative contributions of various mechanisms that are likely to cause aberrant activation of T and B cells during chronic HIV-1 infection remain incompletely understood and are a matter of much debate and speculation. Although chronic immune activation has convincingly been shown to be a major determinant of HIV disease progression and despite the clear evidence that direct or indirect effects associated with HIV viremia and/or HIV replication fuel chronic immune activation, it is likely that multiple factors contribute to this phenomenon.

As discussed here, the aberrant activation of T cells during chronic HIV-1 infection may rely on antigen-dependent as well as antigen-independent mechanisms that are both promoted by the proinflammatory milieu present during HIV infection, either fostered directly by the virus or via secondary effects such as microbial translocation. A detailed analysis of the antigen specificities of activated T cells is required to dissect in more detail how the proinflammatory milieu during HIV infection in combination with increased exposure to (gut) microbial products translates into persistent T cell activation.

Albeit antigen-dependent mechanisms underlying B cell hyperactivation and hypergammaglobulinemia cannot be completely excluded, the majority of existing data argue for a polyclonal activation independent of BCR specificity.

In conclusion, it is very likely that multiple mechanisms contribute to the aberrant T and B cell activation during HIV infection. Nevertheless, it is very important to identify these mechanisms in more detail in order to develop means to interfere with aberrant chronic immune activation, which is clearly a major contributor to HIV pathogenesis.

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