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FULL MANUSCRIPT

Recovery of Interleukin-17 Production from Interleukin-15-Stimulated CD4+ Mononuclear Cells in HIV-1-Infected Patients with Sustained Viral Suppression

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Interleukin-17 (IL-17) is a pro-inflammatory cytokine that is mainly produced by CD4+ T cells. The role of Th17 during the human immunodeficiency virus (HIV)-1 infection is still unclear, but HIV-1 infection can cause a preferential depletion of Th17 cells. It has been shown that IL-15 elicits IL-17 production from human peripheral blood mononuclear cells. We studied the effect of IL-15 stimulation *in vitro* on IL-17 production from CD4+ mononuclear cells of HIV-infected patients. We observed that IL-15 triggers, in a dose-dependent manner, IL-17 secretion. This effect was blocked by anti-IL-15 monoclonal antibody ($P = 0.01$). Interestingly, IL-17 production was significantly lower in patients with detectable plasma viremia when compared with successfully treated HIV-infected patients ($P = 0.02$) and healthy controls, respectively ($P < 0.001$). We also noticed a significant difference in IL-17 production between naïve HIV-infected patients and patients with virological failure on combined antiretroviral therapy (cART) ($P = 0.02$). Our results suggest that IL-15 can induce IL-17 production from peripheral CD4+ mononuclear cells of HIV-infected patients. Persistent HIV plasma viremia could cause a severe perturbation of IL-17 production from CD4+ mononuclear cells. IL-17 production in HIV-infected patients could be recovered through a sustained suppression of the viral replication in the peripheral blood through cART.

Introduction

Interleukin-17 (IL-17) is a pro-inflammatory cytokine that is mainly produced by a new class of effector CD4+ T lymphocytes (Harrington and others 2005). Th17 lymphocytes constitute a recently characterized subset of T-helper cells that are characterized by the secretion of a distinct pattern of cytokines: IL-17A, IL-17F, IL-21, IL-22, and IL-26 (Wilson and others 2007).

Th17 lymphocytes are involved in the induction of a protective immune response against a variety of bacteria and fungi, including human immunodeficiency virus (HIV)-associated opportunistic pathogens. The ability to indirectly induce the recruitment of neutrophils highlights the role of the Th17 cells as a linking bridge between innate and adaptive immune response (Matsuzaki and Umemura 2007; Rudner and others 2007; Pelletier and others 2010; Gaffen and others 2011). The clinical importance of the Th17 cells has been clearly described in Hyper-IgE syndrome (HIES) (Milner and others 2008). This rare primary immune deficiency is characterized by: mutations in the gene encoding STAT3, decreased number of Th17 lymphocytes, and, subsequently, a low level of IL-17. Patients affected by HIES suffer from frequent bacterial and fungal infections, as seen during the HIV-1 infection (Freeman and Holland 2010).

IL-1β, IL-23, transforming growth factor-beta (TGF-β), and IL-6 are considered key factors for the development and the proliferation of Th17 cells (Acosta-Rodriguez and others 2007; Volpe and others 2008).

Recently, a new strong relationship between Th17 and IL-15 has been demonstrated in several autoimmune diseases such as rheumatoid arthritis and psoriasis (Ziolkowska and others 2000; Elder 2007; Hot and Miossec 2011). Moreover, IL-15 induces the strongest production of IL-17 from human peripheral blood mononuclear cells (PBMCs) when compared with IL-2 and IL-23 (Hoeve and others 2006).

Our group is particularly interested in the effect of IL15 on the immune cells during HIV infection. IL-15 is a pleiotropic cytokine with a broad range of biological functions in many diverse cell types that plays a pivotal role in the modulation

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of immune cells of both the innate and adaptive immune systems and in the inflammatory and protective immune responses. From a molecular point of view, IL-15 is a 14–15 kDa glycoprotein that is encoded by a 34 kb region on human chromosome 4q31. Its receptor is composed of a β subunit (IL-2R/15Rβ) that is shared with the IL-2 receptor, a common γ subunit (γc) shared with IL-2, IL-4, IL-7, IL-9, and IL-21, and a unique α subunit (IL-15Rα) which confers receptor specificity to IL-15 (Steel and others 2012). IL-15 mRNA is expressed by multiple tissues (skeletal muscle, kidney, lung, heart, and placenta) and numerous cell types through various stimulatory conditions, including fibroblasts, keratinocytes, epithelial cells of various tissues, nerve cells, monocytes, macrophages, T cells, and dendritic cells (DCs) (Anderson and others 1995; Waldmann and Tagaya 1999; Steel and others 2012). Although IL-15 mRNA expression is widespread, detection of IL-15 protein is largely limited to DCs and monocytes/macrophages. This indicates that, although transcriptional control of IL-15 is important (transcription, translation, and intracellular trafficking stages), the principle level of IL-15 regulation appears to be posttranscriptional. IL-15 protein is post-transcriptionally regulated by multiple controlling elements that impede translation, including 12 upstream adenine, uracil, guanine of the 5′ untranslated region, 2 unusual signal peptides, and the C-terminus of the mature protein (Fehniger and Caligiuri 2001). Finally, a large variety of stimuli induce IL-15 expression and/or release, including lipopolysaccharide and other bacterial products, fungi, viruses, and double-stranded RNA (D'Acquisto and others 2010). From a functional point of view, IL-15 is to act on several immune cells as CD4+ T cells, CD8+ T and NK cells inducing the expansion as well as the production of different cytokines and chemokines. We have already demonstrated the potential role of IL-15 in enhancing the NK cells response against HIV-1 infection *in vitro* (d'Ettorre and others 2006, 2011).

In the present article, we evaluated the effect of the IL-15 stimulation *in vitro* on the secretion of IL-17 from human CD4+ mononuclear cells isolated from HIV-infected patients with distinct clinical and virological characteristics.

Patients and Methods

Study participants included a total of 15 HIV-infected patients and 5 healthy controls from the Department of Public Health and Infectious Diseases of Sapienza University of Rome. Five HIV-infected patients were naive for antiretroviral drugs and presented median CD4+ cell count of 689 cells/mm^3 (range 501–1,076 cells/mm^3) and median viral load (VL) of 3,514 HIV RNA copies/mL (range 52–17,000 cp/mL); five HIV-infected patients treated with combined anti retroviral therapy (cART) presented sustained viral suppression (<50 copies/mL) and median CD4+ cell count of 700 cells/mm^3 (range 314–1,164 cells/mm^3) at the time of the blood draw (cART success). Five HIV-infected patients considered cART failures, presented a median CD4+ count of 325 cells/mm^3 (range 179–654 cells/mm^3) and median plasma VL of 3,000 HIV RNA copies/mL (range 189–4,159 cp/mL). All the patients had received a combination of protease inhibitors or a non-nucleoside reverse transcriptase inhibitor with 2 nucleoside or nucleotide reverse transcriptase inhibitors for 48–184 weeks. No evidence of active opportunistic infections was found at the time of blood sample handling. All individuals signed informed consents approved by the Institutional Review Board of University of Rome "Sapienza," Rome, Italy.

PBMCs from blood of HIV-uninfected and HIV-infected subjects were prepared using Hypaque–Ficoll density centrifugation (Accuprep). CD4+ mononuclear cells were isolated staining PBMCs with biotinylated anti-CD8 followed by avidin-coated magnetic beads and purified over an MACS® column (Miltenyi Biotech), following the manufacturer's instructions. Cell purity was >95%$^+$, as measured by flow cytometry. Freshly isolated CD4+ mononuclear cells (5×10^5/mL) were cultured in 24-well plates in Roswell Park Memorial Institute (culture medium) 1640 supplemented with 2 mM L-glutamine, 10% fetal calf serum (Seromed), 100 U/mL penicillin, 100 μg/mL streptomycin, and 1 mM hydroxyethylpiperazine ethanesulafonic acid at 37°C in an atmosphere of 95% air and 5% CO_2. Cells were stimulated for 72 h in the presence or absence of a mixture of phorbol myristate acetate (1 nM) and ionomycin (3 μg/mL), or cytokine: IL-15 (0, 1–100 ng/mL; Immunex). To study the effect of neutralizing anti-IL-15 monoclonal antibody (mAb) on IL-15-induced production of IL-17, recombinant human IL-15 (100 ng) was incubated with or without anti-IL-15 mAb (M111, 3 μg) or normal mouse mAb (3 μg) for 30 min at 37°C before addition to cell cultures. After incubation, culture supernatants were collected by centrifugation at 400*g* for 10 min, and concentrations of IL-17 were determined using human IL-17 enzyme-linked immunosorbent assay (ELISA) kit (R&D System). The lowest limit of detection was 15 pg/mL for IL-17.

Moreover, with the aim of evaluating whether the *in vivo* levels of both IL-15 and IL-17 were compromised in individuals with HIV infection, we determined the levels of these cytokines in plasma samples from the study subjects. The cytokine plasma levels were determined by ELISA methodology. In the same way, we evaluated the fraction of Th17 cells present among CD4+ T cells of each subject, by flow cytometry.

Data are expressed as mean ± standard error of the mean. Statistical significance was evaluated using paired Student's *t*-test for the *in vitro* experiments. The concentrations of IL-17 released by CD4+ mononuclear cells were analyzed by nonparametric Mann–Whitney Rank Sum test, using Graphpad Prism 4 software (Graphpad Software Inc.). Probability values <0.05 were considered statistically significant.

Results

We stimulated freshly isolated CD4+ mononuclear cells from healthy subjects with an increasing concentration of IL-15 in order to detect IL-17 production *in vitro*. The stimulation *in vitro* with an increasing amount of IL-15 induced a statistically significant and dose-dependent increase in the production of IL-17 by CD4+ mononuclear cells. The addition of monoclonal anti-IL-15 antibody significantly reduced the secretion of IL-17 from the CD4+ mononuclear cells isolated from the healthy donors when stimulated with IL-15 50 and 100 ng/mL ($P=0.04$ and 0.01, respectively; Fig. 1).

We then evaluated the effects of IL-15 stimulation *in vitro* on IL-17 secretion from CD4+ mononuclear cells of HIV-infected patients. We observed a significant difference in IL-17 secretion *in vitro* from IL-15 stimulated CD4+ mononuclear cells of HIV-infected patients with detectable VL when compared with IL15-stimulated CD4+ cells of

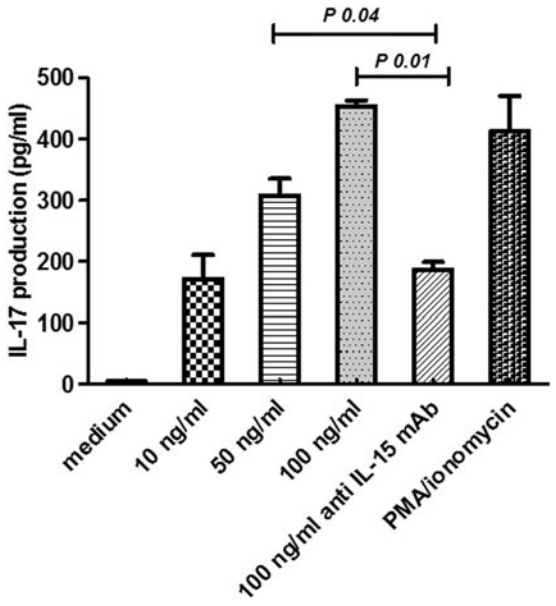

FIG. 1. The stimulation with IL-15 induces IL-17 production from CD4+ mononuclear freshly isolated from human PBMCs and is influenced by the HIV viremia. IL-17 concentrations in the supernatant fluids of freshly isolated human CD4+ mononuclear cells (5×10^5/mL) incubated for 72 h with or without IL-15 (10 mg/mL, 50 ng/mL, and 100 ng/mL) or anti-IL-15 mAb (M111, 3 ng/mL) in conditioned medium and PMA/ionomycin. Stimulation with increasing amounts of IL-15 triggers, in a dose-dependent manner, IL-17 production from CD4+ mononuclear cells of healthy controls ($n=5$). The addition of anti-IL-15 monoclonal antibody significantly reduces IL-17 production from CD4+ T mononuclear cells previously stimulated with IL-15 (100 ng/mL). Medium contained no stimulus. Cytokine concentrations in the conditioned medium were expressed in pg/mL and were determined by ELISA. Data are expressed as mean ± standard error of the mean (SEM). Only significant P values are shown. IL-17, interleukin-17; PBMCs, peripheral blood mononuclear cells; HIV, human immunodeficiency virus; anti-IL-15 mAb, anti-interleukin-IL-15 monoclonal antibody; PMA, phorbol myristate acetate; ELISA, enzyme-linked immunosorbent assay.

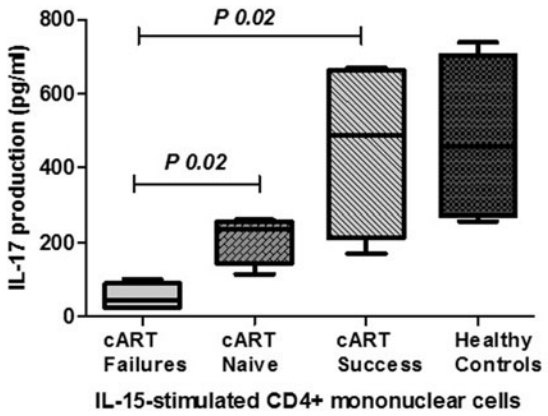

FIG. 2. IL-17 production from CD4+ mononuclear cells of HIV-infected patients. IL-17 concentrations (pg/mL) were compared among HIV-positive patients with virological failure to cART (cART failures, $n=5$), patients naive to cART (cART naive, $n=5$), patients with undetectable viral load after cART (cART success, $n=5$), and HIV-negative individuals (healthy controls, $n=5$). IL-17 concentrations in supernatant fluids of freshly isolated CD4+ mononuclear cells (5×10^5/mL) incubated for 72 h with IL-15 (50 ng/mL) in conditioned medium. Cytokine level in the conditioned medium is expressed in pg/mL and was determined by ELISA. Data are expressed as mean ± SEM. Only significant P values are shown. cART, combined antiretroviral treatment.

HIV-infected subjects with undetectable VL ($P=0.02$) and healthy controls ($P<0.001$), respectively (data not shown). To study the effect of HIV infection on IL-17 production, we separated the HIV-infected patients on the basis of their immunological and virological characteristics. We noticed a statistically significant increased production of IL-17 from CD4+ mononuclear cells of HIV-infected patients with undetectable VL during cART when compared with HIV-infected patients presenting virological failure in cART ($P=0.02$). Interestingly, IL-15 stimulated CD4+ mononuclear cells of HIV-infected patients who were naïve to anti-retroviral treatment demonstrated a significant difference in IL-17 secretion when compared with CD4+ cells from the patients with virological failure ($P=0.02$; Fig. 2). There was no significant difference in IL-17 secretion between CD4+ mononuclear cells from HIV-infected naïve patients and HIV-infected patients with undetectable VL during cART.

Plasma IL-15 levels (measured *in vivo*) were significantly elevated in cART failure group (9.93 ± 2.64 pg/mL) compared with cART success group (5.65 ± 2.69 pg/mL), naive subjects (6.88 ± 1.97 pg/mL), and healthy controls (3.62 ± 1.42 pg/mL) ($p<0.05$). On the other hand, plasma IL-17 levels were statistically significantly lower in HIV patients with cART failure (16.12 ± 0.26 pg/mL) than those in patients with cART success (26.88 ± 2.26 pg/mL), in naive subjects (19.68 ± 1.25 pg/mL), and in healthy controls (31.24 ± 0.66 pg/mL) ($p<0.05$). In the same way also, the percentage of Th17 cells to total CD4+ T cells was 1.6% ± 0.37% in patients before treatment, which was significantly lower than that in cART success group (3.9% ± 0.42%), in naïve group (2.78% ± 0.37%), and in uninfected controls (5.74% ± 0.4%). Moreover, the percentage of Th17 cells positively correlated with IL-17 levels ($r=0.98$, $p=0.001$) (Table 1).

Discussion

The aim of this study was to investigate the potential effect of IL-15 stimulation *in vitro* on the production of IL-17 by CD4+ mononuclear cells of HIV-infected patients. We initially confirmed that IL-15 presents a dose-dependent effect on IL-17 production from CD4+ cells of healthy donors. It has been shown that IL-15 has the ability to expand a subpopulation of CD4+ T cells which are able to produce IL-17 (El Hed and others 2010). Moreover, IL-15 proved to strongly induce IL-17 production by human T cells, especially when compared with other cytokines such as IL-2 and IL-23 (Hoeve and others 2006). IL-15 enhances T-cell proliferation and homeostasis through a variety of intracellular events involving the activation of intracellular signaling molecules such as Janus Kinase-3 and signal transducers and activators such as STAT-5 and STAT-3 (Johnston and others 1996; Giron-Michel and others 2003). The latter nuclear transcription factor is also critical for IL-6 and TGF-β-induced differentiation of Th17 cells (Yang and others 2007). Thus, it is likely that IL-15

Table 1. Plasma Interleukin-15 and Interleukin-17 Levels Measured *In Vivo* and Fraction of Th17 Cells Present Among CD4+ T Cells of Subjects Enrolled

Patient	*Group*	*Plasma IL-15 levels (pg/mL)*	*Plasma IL-17 levels (pg/mL)*	*% Th17 cells to total CD4+ cells*
Patient 1	cART success	2.99	24.4	3.7
Patient 2	cART success	7.000	28.3	4.0
Patient 3	cART success	9.292	29.7	4.4
Patient 4	cART success	3.042	24.8	3.3
Patient 5	cART success	5.958	27.2	4.1
Patient 6	cART failure	13.042	16.2	1.2
Patient 7	cART failure	7.208	15.8	1.6
Patient 8	cART failure	9.917	15.9	1.4
Patient 9	cART failure	7.417	16.4	2.2
Patient 10	cART failure	12.09	16.3	1.6
Patient 11	Naive for cART	9.220	19.3	2.7
Patient 12	Naive for cART	6.333	19.1	2.8
Patient 13	Naive for cART	8.667	20.7	3.1
Patient 14	Naive for cART	5.470	21.2	3.1
Patient 15	Naive for cART	4.710	18.1	2.2
Patient 16	Healthy control	2.99	31.1	5.3
Patient 17	Healthy control	2.99	30.9	5.7
Patient 18	Healthy control	2.99	32.1	6.1
Patient 19	Healthy control	6.167	30.4	5.4
Patient 20	Healthy control	2.99	31.7	6.2

IL, interleukin; cART, combined antiretroviral therapy.

induces a dose-dependent IL-17 production from human CD4+ mononuclear cells in a STAT-3-dependent manner. The question whether IL-15 has direct effects in modulating the synthesis of IL-17 or whether the effects of IL-15 in altering the functions of Th17 population are indirect is still open. Anyway, a recent article of Harris provided primary evidence that IL-15 promotes Th17 and Th1 responses by skewing monocytes into IL15-DCs. In fact, this author showed that (1) IL15-DCs (DCs generated from monocytes using granulocyte/macrophage colony stimulating factor with IL-15) produced high levels of IL-1β and IL-15 in response to TLR4 stimulation; (2) IL15-DCs stimulated with TLR agonists secreted significantly higher concentrations of the Th17-promoting factors, IL-1β, IL-6, IL-23, and CCL20, and lower levels of the Th1 cytokine, IL-12; (3) IL15-DCs primed with TLR3 or TLR4 agonists triggered Th17 (IL-17, IL-22, and/or IFN-γ) and Th1 (IFN-γ) responses; and (4) secretion of IL-17 and IFN-γ required contact with TLR-primed IL15-DCs (Harris 2011). Moreover, Lee and others (2010) evidenced that (1) human Th17 cell differentiation is regulated via differential expression of IL-1RI, which is controlled by IL-7 and IL-15; (2) the differential expression of IL-1RI on human $CD4^+$ T cells confers distinct capacities in producing IL-17, and such cytokine receptor expression is dynamically regulated via T-cell receptor triggering and cytokines, including IL-7, IL-15, and TGF-β.

In our opinion, IL-17 secretion from CD4+ mononuclear cells in the peripheral blood could be partially restored while beginning a successful antiretroviral treatment and controlling HIV viral replication. Although the clinical characteristics of our selected population may have influenced the response to IL-15 stimulation *in vitro*, we noticed that the IL-17 secretion from the CD4+ mononuclear cells of patients with virological failure was significantly lower than in HIV-infected patients who were successfully treated and healthy donors. We did not observe any significant difference in IL-17 secretion from CD4+ mononuclear cells of healthy donors and HIV-infected patients with undetectable VL, although IL-17 production was lower in the latter. HIV-1 infection can cause a multifaceted alteration of Th17 cells, directly through the infection of activated CD4+ CCR5+ and CCR6+ T cells, which represent a large percentage of IL17-producing T cells (El Hed and others 2010). In addition, HIV-induced systemic immune activation indirectly creates an immunological imbalance, which results in polarization toward other T-helper subsets (El Hed and Unutmaz 2010). Recent studies support our hypothesis, as the complete suppression of HIV viremia in HIV-infected children induced an increased IL-17 production (Ndhlovu and others 2008). Moreover, partial but significant repopulation of IL-17-producing cells in the sigmoid mucosa of HIV-infected patients has been shown after a long-term anti-retroviral treatment (Chege and others 2011).

Interestingly, a significant difference in IL-17 secretion was found between the CD4+ mononuclear cells of HIV-infected patients who were cART-naïve with detectable VL when compared with HIV-infected patients with detectable HIV viremia failing the cART. One important difference between these two groups of individuals was the higher number of CD4+ T-cells in HIV-infected patients who were naïve to cART than the HIV-positive subjects with cART failure. In addition, in our opinion, the preserved functionality and plasticity of CD4+ T lymphocytes of the naïve subjects could have prompted an adequate response to the *in vitro* stimulation with IL-15. This finding is in line with recently published data showing the persistence of Th17 population in long-term-non-progressors HIV-infected patients in the peripheral blood and in the gut mucosa (Chege and others 2011; Ciccone and others 2011; Salgado and others 2011). The preservation of this subset of effector T lymphocytes may reflect the lower level of immune activation and disease progression in this population of HIV-infected patients.

Finally, the impaired *in vivo* levels of both IL-15 and IL-17 (measured in plasma samples) from the HIV subjects demonstrate that the levels of these cytokines are compromised in individuals with HIV infection; these data represent a further support for the idea that there is a real correlation between upregulation of IL-17 production by IL-15. Moreover the observation that the percentage of Th17 cells positively correlated with IL-17 levels evidences the fact that the reduction in IL-17 production is simply parallel to the reduction in Th17 cells (Fig. 3).

Our results in plasma samples are in some way contradictory compared with those obtained *in vitro*; however, the fact that apparently higher levels of IL-15 induce *in vivo* lower levels of IL-17 may be attributable to factors currently not known that may reduce the effectiveness of IL-15 in patients with non-suppressed VL. In fact, it is possible that, *in vivo*, higher levels of IL-15 are required to obtain a corresponding increase of IL-17 in viremic patients. At the moment, in every case, the interpretation of the data is purely speculative, as the way in which the IL-15 modulates the function of Th17 and the synthesis of IL-17 remains an open question.

There are some limitations in our study that need to be considered. First, our findings need to be confirmed in large

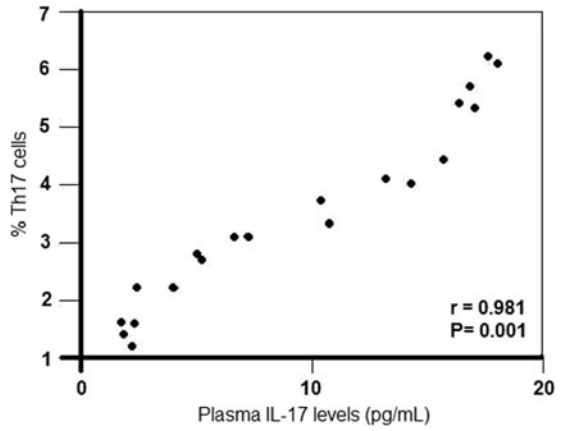

FIG. 3. Correlation between the percentage of Th17 and the IL-17 plasma levels. The *in vivo* results showed that the percentage of Th17 cells positively correlated with IL-17 plasma levels.

cohort studies, given the small sample of the population studied. Second, a prospective study on the possible recovery of IL-17-producing T cells after the introduction of cART may provide further information. In addition, it is now known that several different cell types, including the NK T cells, are capable of producing IL-17. We did not evaluate the effect of *in vitro* IL-15 stimulation on freshly isolated CD4+ T cells, NK T cells, and also Th17 isolated from the gut mucosa, which represent an important reservoir of these effector cells. In fact, HIV-1 infection induces the depletion of Th17 in the peripheral blood as well as in the gut mucosa (Cecchinato and others 2008; Prendergast and others 2010). Moreover, the preservation of IL-17-producing T lymphocytes in the gut mucosa is associated with a slower progression of the disease (Ciccone and others 2011). Therefore, it would be interesting to study the effect of *in vitro* IL-15 stimulation on the different cell types in a different immunological environment in HIV-infected patients. Finally, although recent studies have shown a controversial role of IL-15 during acute HIV and simian immunodeficiency virus infections, its effect during the chronic phase of HIV infection is still under observation. The ability of IL-15 to expand different CD4+ T-cell subpopulations in the animal model and the possibility to direct the NK cell response *in vitro* against HIV-infected cells emphasizes the importance of continuing the study of this cytokine.

Conclusions

In summary, we show that IL-15 can induce the secretion of IL-17 from human CD4+ mononuclear cells of healthy controls and HIV-infected patients. We demonstrated that the plasma HIV-1 viremia could influence IL17 secretion. These findings support the hypothesis that a successful suppression of HIV-1 viral replication below the detectable level could allow a partial restoration of Th17 cells. Thus, the relationship between IL-15 and Th17 and their role in the progression of HIV-1 infection needs further evaluation.

Acknowledgments

L.Z. designed and performed the experiments and wrote the article; G.D.E. and G.C. was involved in the study design and wrote the article. M.A., G.C., N.G., and S.M. performed the experiments. T.A. identified and recruited patients for the study. C.M.M. and G.C. reviewed and provided revision to the final article. S.V and V.V. were grant holders and provided revision to the final article.

Author Disclosure Statement

No external funding was received for this work; no conflict of interest.

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