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Endothelial Dysfunction in HIV Infection – The Role of Circulating Endothelial Cells, Microparticles, Endothelial Progenitor Cells and Macrophages

Mariola López[1], Jesús San Román[2], Vicente Estrada[3], Eugenia Vispo[1], Francisco Blanco[1] and Vicente Soriano[1]

[1]Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain; [2]Department of Medicine, Medical School, University Rey Juan Carlos I, Madrid, Spain; [3]HIV Unit, Hospital Clínico San Carlos, Madrid, Spain

Abstract

Endothelial dysfunction has emerged as one of the major mechanisms involved in the increased cardiovascular disease risk seen in the HIV population. Endothelial progenitor cells, circulating endothelial cells, endothelial microparticles, and platelet microparticles are all now considered as biomarkers of cardiovascular disease risk in otherwise healthy individuals. Preliminary evidence suggests that these biomarkers may similarly predict cardiovascular disease risk in HIV-infected patients, helping to assist in preventive and therapeutic decision making. This review updates the current knowledge and the most recent advances in the pathophysiology of cells and particles involved in atherosclerosis in the HIV setting. The potential usefulness of measuring cardiovascular disease risk biomarkers in HIV-infected individuals to prevent future cardiovascular events is further discussed. **(AIDS Rev. 2012;14:223-30)**

Corresponding author: Mariola López, mariolalopezvazquezdelatorre@msn.com

Key words

Atherosclerosis. Endothelial progenitor cell. Circulating endothelial cell. Endothelial microparticle. Macrophage activation.

Introduction

Besides causing immunodeficiency, HIV infection is characterized by hyperactivation of the immune system and chronic inflammation. In this regard, HIV infection might potentiate other chronic inflammatory diseases such as atherosclerosis. Recent studies have demonstrated that HIV infection induces a pro-thrombotic state and pro-inflammatory phenomena in the vascular endothelium, leading to increased cardiovascular disease risk (CVDR) independently of traditional risk factors[1] (Fig. 1). Moreover, high plasma HIV RNA levels have been associated to endothelial dysfunction, which is a well-established predictor of atherosclerosis[1-3]. More recently, an increased rate and severity of coronary atherosclerosis has been found in asymptomatic, HIV-infected young men with long standing HIV disease compared with uninfected subjects[4].

Vascular integrity results from the equilibrium between mechanisms of vascular damage and repair. The injury of blood vessels is associated with high levels of circulating endothelial cells (CEC) and microparticles (MP) from endothelium (EMP) and platelets (PMP). Under normal conditions, the processes involved in the restoration of the vascular integrity mainly imply the activity of progenitor cells, plaque neovascularization, and reverse cholesterol transport[5]. Interestingly, all these mechanisms seem to be impaired in HIV-infected individuals. Uncontrolled HIV replication is associated with high levels of CEC and MP, all of which are surrogates of vascular damage. Altogether, these findings support that HIV replication drives disequilibrium in the atherosclerosis process, favoring a misbalance in favor of proatherogenic

Correspondence to:
Mariola López
Laboratorio de Biología Molecular
Servicio de Enfermedades Infecciosas
Hospital Carlos III
Sinesio Delgado, 10
28029 Madrid, España
E-mail: mariolalopezvazquezdelatorre@msn.com

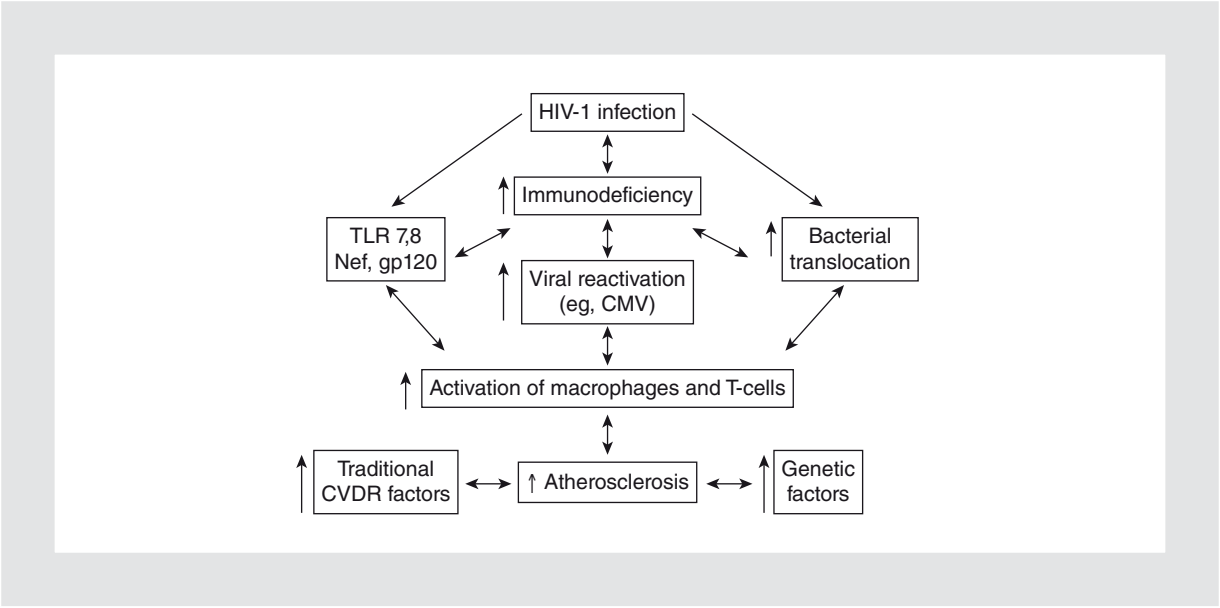

Figure 1. *Factors involved in the interaction between atherosclerosis and HIV infection. CMV: cytomegalovirus; CVDR: cardiovascular disease risk.*

events. The restoration of proper dynamics that may ameliorate vascular damage in HIV patients requires a better understanding of the pathophysiology of these cells and particles during the course of infection.

Endothelial repair by endothelial progenitor cells is impaired in HIV infection

In 1997 Asahara, et al. identified a distinct subset of cells in the peripheral blood involved in the renewal of the vascular endothelium[6]. These were named endothelial progenitor cells (EPC). Since then, several studies conducted in HIV-negative patients have demonstrated an inverse association between the amount of these cells and CVDR[7,8].

The link between EPC deficiency and CVDR has been demonstrated at different stages of the atherosclerotic process[9,10]. Moreover, EPC levels have been inversely correlated with the number of distinct cardiovascular risk factors in coronary artery disease[7], supporting that EPC are a good surrogate marker of cumulative cardiovascular risk. Endothelial progenitor cells are key determinants of endothelial dysfunction[11] and show a high predictive value of early vascular disease, even better than traditional risk factors[12]. In this regard, a recent study has shown that the cumulative event-free survival rate at one year directly increases with baseline EPC levels in patients with cardiovascular arterial disease[13].

Under normal conditions, as a consequence of endothelial injury, EPC increase to repair the damaged vascular endothelium (Fig. 2 A). This physiological process is altered in the setting of HIV infection, although only few studies have so far examined EPC levels in HIV-infected patients. Recently, two separate studies have demonstrated that young, drug-naive, HIV-positive individuals with low CVDR have lower EPC levels in comparison to HIV-negative subjects with similar age and traditional cardiovascular risk factors[14,15]. This observation contrasts with results from another study testing a similar population of HIV-infected individuals, in which the average amount of EPC was not significantly decreased in comparison to healthy controls[16]. However, although differences in mean EPC levels were not statistically significant, a clear trend was noticed for lower EPC in HIV-positive persons than in controls. Thus, most recent data support that the increased CVDR associated with HIV infection may be attributed to reduced EPC levels. In this regard, the endothelial dysfunction characteristically seen in HIV infection may result from an impaired effective vascular restoration (Fig. 2 B). As a result, the mechanisms mediated by EPC that protect against development of atherosclerosis could be impaired in HIV infection.

Hypothetically, HIV infection might decrease the number of EPC by a direct infection of these cells. The EPC phenotype is characterized by the expression of the

chemokine receptors CCR5 and CXCR4 on the cell surface, allowing potential HIV infection of these cells. Indeed, a recent study has demonstrated that circulating colony-forming unit-endothelial cells (CFU-EC) are infected by HIV[17]. According to our data[15] and results from others[14], EPC could be a subset of CFU-EC. Therefore, direct infection of EPC by HIV might explain their reduced amount in the presence of uncontrolled viral replication. Interestingly, the use of potent antiretroviral therapy may restore EPC levels even above levels seen in healthy controls[18]. Future research must focus on the impact of antiretroviral therapy on EPC, conducting longitudinal studies.

Endothelial damage by circulating endothelial cells and microparticles is increased in HIV infection

Circulating endothelial cells are mature endothelial cells discarded from the endothelium in response to vascular damage[19]. Increased levels of CEC have been associated to elevated plasmatic endothelial dysfunction markers such as Von Willebrand factor levels[20] and with abnormal vascular responses induced by low-flow mediated dilatation[21]. In this regard, high amounts of CEC reflect endothelial damage and high CVDR.

Similar to CEC, microparticles from endothelium (EMP) and from platelets (PMP) have been proposed as biomarkers of endothelial dysfunction[22]. Microparticles of 0.1-2 μm in size are phospholipid and protein-rich submicron molecules originating from the membrane of multiple cells (platelets, leucocytes, erythrocytes, and endothelial cells) in response to cellular activation and/or apoptosis. On their surface, MP expresses proteins of cells from which they came, allowing their characterization. Increased numbers of EMP and PMP have been noticed in patients with high CVDR[23-25]. Thus, vascular damage is generally associated with high levels of CEC, EMP, and PMP.

Two recent studies have examined the level of CEC[15], EMP and PMP[14,26] in patients with uncontrolled HIV infection. Interestingly, the proportion of CEC and the amount of EMP were significantly increased in HIV-infected individuals compared to healthy controls with similar ages. Altogether, these findings suggest that a reduced effect of CEC and EMP on the restoration of endothelial damage might potentiate CVDR in HIV infection independently of traditional cardiovascular risk factors. Table 1 records the list of biological mechanisms that contribute to abnormal vascular integrity in HIV infection.

Table 1. Mechanisms involved in the alteration of vascular integrity in HIV infection

- Reduction and dysfunction of EPC
- Increase of CEC
- Increase of EMP
- Increased microbial translocation
- High levels of proinflammatory mediators
- Hyperactivation of macrophages and T-cells
  - Increased expression of soluble CD163
  - High tissue factor levels
- Reduction of reverse cholesterol transport
  - Reduction and dysfunction of HDL
  - Down-modulation of ABCA1 by Nef

EPC: endothelial progenitor cells; CEC: circulating endothelial cells; EMP: endothelial microparticles; HDL: high-density lipoprotein.

Although PMP levels seem to be similar in HIV-infected individuals and healthy subjects, levels of activated PMP are increased in the subset of HIV-infected patients on antiretroviral therapy[27] and in untreated HIV-infected patients[26]. This fact results from the existence of two different subsets of PMP, one of which is represented by activated PMP. This subset of cells might be a more sensitive marker of CVDR, being increased even in patients with suppressed HIV replication due to antiretroviral therapy. Similar studies testing the impact of suppressed viremia due to antiretroviral therapy on CEC and EMP are lacking, and therefore their influence on vascular integrity is unknown in this situation and warrants further investigation.

Misbalance in vascular integrity as a result of uncontrolled HIV replication

Under normal conditions, the endothelial vascular integrity results from a balance between endothelial damage and repair. Any variation in this equilibrium may result in damage of the endothelium integrity. In order to estimate the extent of endothelial dysfunction, several indexes have been developed, most of which consider EPC and injury markers[28,29]. Conditions associated with increased CVDR generally go with depletion of cells involved in the reparation of endothelium. A combination of high levels of EMP and/or CEC along with reduced EPC levels impairs the necessary compensatory responses favoring atherosclerosis and develops and progresses.

A reduced activity of EPC in HIV infection may result in insufficient endothelial repair. Likewise, an increase in CEC, EMP and activated PMP levels, all of which are involved in endothelial injury, might contribute to the accelerated vascular disease progression characteristically seen in HIV-infected patients (Table 1). No studies so far have assessed the consideration of these four parameters together in the prediction of CVDR in HIV infection. However, two separate reports have shown a misbalance between repair mechanisms mediated by EPC and endothelial damage associated to CEC or EMP in uncontrolled HIV replication[14,15]. The mechanism by which HIV increases the number of CEC and also EMP is unknown. HIV replication might induce the activation of endothelial surfaces directly or via upregulation of proinflammatory mediators[30,31]. This effect could lead to endothelium injury with release of CEC and activated PMP. This process, along with the possibility of direct HIV infection of EPC, might induce apoptosis of EPC and, as a consequence, increased release of EMP. At this time, the contribution of each apoptotic endothelial cell subset to the total EMP level is unknown. Longitudinal studies examining both quantitative and qualitative aspects of EPC, CEC, activated PMP and EMP are warranted in HIV-infected patients.

Hyperactivated macrophages and plaque vulnerability in HIV infection

Activated macrophages are a key component of the atherosclerotic process and have been shown to migrate towards the atherosclerotic plaque[32]. In this regard, the activation of the innate immune system contributes to cardiovascular disease. The macrophages get out of lipid-rich plaques and stabilize atherosclerotic plaques[33]. However, plaque neovessels can break easily, allowing for extravasation of erythrocytes[33]. Lysis of red cells contributes to lipid expansion, release of free hemoglobin (free-Hb) and reactive oxygen species (ROS) and ultimately to lipid peroxidation and macrophage activation within the atherosclerotic plaque. However, free-Hb links to haptoglobin (Hp) forming Hp-Hb complexes, which are cleared by the macrophage receptor CD163[34]. Thus, the ability of macrophages to remove Hp-Hb complexes may influence plaque stability.

Soluble CD163 (sCDC163) is shed via proteolytic cleavage at the monocyte/macrophage surface. It is released in plasma in response to lipopolysaccharide (LPS) and oxidative stress mediators[35,36]. In this regard, sCD163 has also been proposed as a surrogate biomarker of coronary atherosclerosis[37].

HIV infection is characterized by a hyperactivation of both innate and acquired immune systems, including macrophages, natural killer, natural killer T-cells, B-cells, and T-cells among others. In early studies, T-cell activation associated to atherosclerosis was intensively examined in HIV-infected patients. T-cell activation in untreated HIV-infected patients is indirectly associated with a high carotid artery intimamedia thickness, a well-established index of subclinical atherosclerosis[38,39]. Moreover, T-cell activation has been correlated with endothelial dysfunction, high levels of procoagulant tissue factor[40], and antigen-specific $CD8^+$ T-cell responses[41].

The interplay between HIV, macrophages, and atherosclerosis has attracted much interest (Fig. 1 and 3). Activated macrophages have been proposed as the link between atherosclerosis and HIV infection[42]. HIV preferentially infects $CD4^+$ T-cells in the gut-associated lymphoid tissue (GALT)[43], inducing a structural alteration of the gastrointestinal mucosa, which results in LPS release to the bloodstream and activation of macrophages[44]. Levels of activated macrophages expressing tissue factor or CD163 in GALT and levels of tissue factor and sCD163 in plasma have been correlated with markers of microbial translocation[40,45]. Based on these findings, high levels of sCD163 might be expected in untreated HIV infection and favor atherosclerosis phenomena. A recent report has highlighted that sCD163 levels are increased in HIV-infected individuals with low or undetectable viremia in comparison with HIV-uninfected subjects[45], and high sCD163 levels are significantly associated with increased non-calcified plaque burden. This plaque modality is the most vulnerable plaque to rupture, regardless of traditional CVDR factors.

The current knowledge of the biological mechanisms involved in the atherosclerosis process in HIV infection is summarized in figure 3. Microbial translocation and HIV replication might enhance the activation of monocytes/macrophages expressing tissue factor and/or CD163 and increase tissue factor and sCD163 in plasma. This process might induce a pro-coagulation state and impaired clearance of Hb-Hp complexes, increasing plaque vulnerability and, indirectly, activation of T-cells. Hyperactivation of T-cells might stimulate further proinflammatory processes and result in endothelial dysfunction. The circle is closed with further stimulation of microbial translocation in GALT, and ultimately increased CVDR.

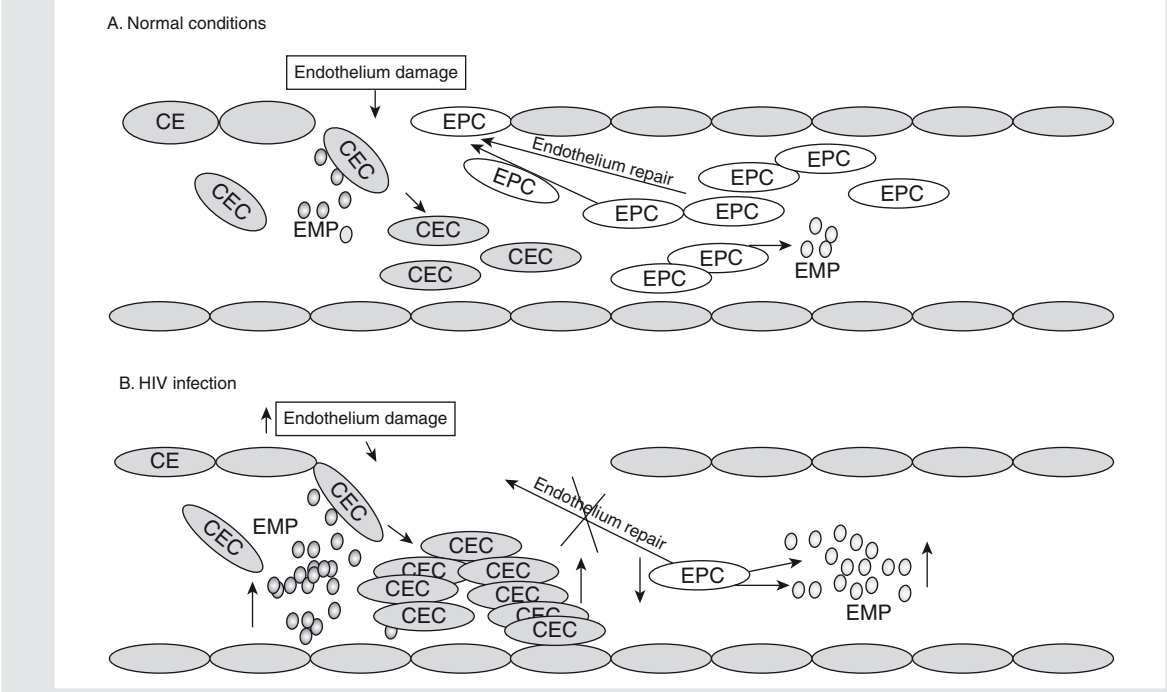

Figure 2. *Vascular integrity results from the equilibrium between endothelial injury and repair. CEC: circulating endothelial cells; EMP: endothelial microparticles; EPC: endothelial progenitor cells.*

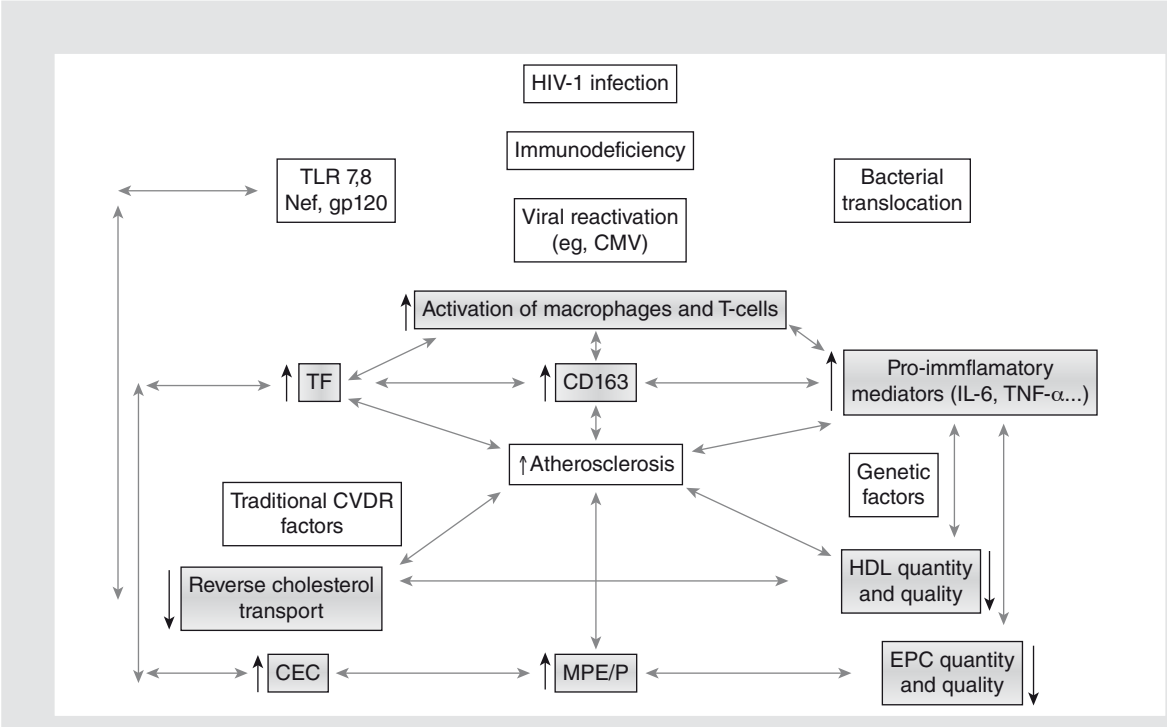

Figure 3. *Novel biological mediators involved in atherosclerosis in HIV infection. Novel biological mediators involved in atherosclerosis in HIV infection are enhanced. CMV: cytomegalovirus; TF: tissue factor; IL-6: interleukin-6; TNF: tumor necrosis factor; CVDR: cardiovascular disease risk; CEC: circulating endothelial cells; MPE/P: microparticles from endothelium and platelets; EPC: endothelial progenitor cells.*

HIV infection drives early cardiovascular disease through its impact on the immune system, leading to chronic inflammation. The macrophage activation that characterizes HIV infection, independently of traditional CVDR factors, contributes to subclinical atherosclerosis, predisposing HIV-infected individuals to plaque rupture and premature cardiovascular disease.

Abnormal reverse cholesterol transport in HIV infection

The last step involved in the repair of damaged blood vessels is reverse cholesterol transport[46], a process by which extrahepatic cholesterol is transported by high-density lipoprotein (HDL) to the liver for excretion throughout the bile and feces. The free cholesterol efflux from macrophages out of the vessel wall occurs mainly by interaction with the ABCA1 transporter. ABCA1-deficient macrophages display significantly reduced reverse cholesterol transport[47]. This is the major mechanism by which HDL could protect against atherosclerosis. The reverse cholesterol transport reflects HDL function and/or quality of HDL. The cholesterol efflux capacity mediated by HDL is only partially estimated by levels of HDL cholesterol or apolipoprotein A-I[48]. Moreover, the cholesterol efflux capacity mediated by HDL is influenced by both the presence and extent of atherosclerosis. These findings reinforce the notion that that the quality of HDL largely influence athero-protection.

HIV infection is associated with abnormalities in the HDL metabolism that could impair reverse cholesterol transporting[49]. Moreover, HIV reduces cholesterol removal from macrophages by downregulation of ABCA1, an effect that is mediated by the viral Nef protein. The consequence of this impaired cholesterol efflux from infected macrophages is an accumulation of cholesterol into these cells, promoting their conversion into foam cells[50]. This finding has been confirmed by examining atheromatous plaques in HIV-infected individuals, taking as comparison uninfected controls. In fact, HIV-infected patients show an increased plaque lipid content with respect to controls[51].

Soluble Nef, which is released from HIV-infected cells, might also affect cholesterol efflux from uninfected cells, including macrophages and hepatocytes[52]. This alternative effect of Nef on atherogenesis could induce alterations in the HDL metabolism, further contributing to increase the CVDR in HIV-infected patients[49] (Table 1).

The effect of antiretroviral agents on reverse cholesterol transport has recently been examined[53]. None of seven compounds affected cholesterol efflux from macrophages at non-cytotoxic concentrations, suggesting that the virus itself is the most likely responsible for the impaired athero-protective pathway (reverse cholesterol transport) characteristically seen in HIV infection.

Statins

Statins are HMG-CoA reductase inhibitors. They reduce atherosclerosis by lowering low-density lipoprotein cholesterol (LDL-c) levels. However, statins do not affect the quality and/or quantity of HDL-c. Statins might also exhibit pleiotropic effects, including antiatherogenic and anti-inflammatory properties. Interestingly, statins mediate the release of EPC from the bone marrow, leading to an increase in the number as well as stimulating these cells[54,55]. In patients treated with atorvastatin with stable coronary artery disease, a 1.5-fold increase in EPC has been recognized[55]. Similar findings have been obtained in patients with chronic heart failure treated with simvastatin[56] and in patients treated with rosuvastatin[57,58].

Statins could enhance endothelial nitric oxide (NO) bioavailability by both promoting endothelial NO production and preventing NO inactivation by free radicals[59]. Nitric oxide derived from endothelial-NO-synthase (eNOs) displays an important role in EPC functionality[60]. Thus, the effects of statins on EPC could be due to an increase in NO bioavailability. However, distinct statins might exhibit differential effects on EPC functions. In this regard, rosuvastatin *in vitro* increases EPC levels, causing an anti-inflammatory polarization of these cells[61]. In injured animal models, simvastatin induces EPC mobilization, contributing to re-endothelization *in vivo*[54]. Likewise, cerivastatin restores the impaired neovascularization characteristically seen with aging[62]. Therefore, further studies are required to elucidate the potential mechanism used by different statins for increasing both the quantity and quality of EPC and their impact on CVDR. Given that no association has been found between markers of inflammation and oxidative stress and the characteristic increase in EPC levels with statins, the mechanism of their effect remains unclear.

In HIV-infected patients, statins reduce LDL-c and diminish the activation of T-cells[63,64], which is a fundamental mechanism involved in the pathogenesis of HIV infection. A recent *in vitro* study has shown that the anti-inflammatory effect of simvastatin on LPS-stimulated macrophages (as it occurs in HIV infection) occurs through inhibition of NOS expression, release of

pro-inflammatory mediators, including tumor necrosis factor-α, nitrite, and free radicals. This effect occurs along with an increase in anti-inflammatory mediators, such as interleukin-10[65]. Thus, there is a potential benefit of statins in HIV-infected patients that goes beyond control of dyslipidemia. Studies examining the effects of statins on cells and molecules involved in the vascular integrity (EPC, CEC, and MP) as well as their influence on inflammation and activation have to be conducted in the HIV setting.

Summary

The interplay between HIV replication, chronic hyperactivation of the innate immune system, systemic inflammation, quantitative and qualitative defects in endothelial cells, abnormalities in the cholesterol metabolism, and subclinical atherosclerosis is being unveiled. Besides classical cardiovascular risk factors, these new parameters, typically altered in uncontrolled HIV replication, may contribute to the increased CVDR typically seen in HIV-infected patients.

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