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Interleukin 18 and Cardiovascular Disease in HIV-1 Infection: A Partner in Crime?

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Abstract

Cardiovascular disease has been frequent in HIV-infected patients both before and after the advent of antiretroviral therapy (HAART). The pathogenic basis for the increase of cardiovascular disease, in particular myocardial lesions, may involve HIV-1 itself or other mechanisms including endothelial dysfunction, activation of proinflammatory cytokines, and changes in platelets, which lead to atherosclerotic lesions of blood vessels. In the last decade, among the proinflammatory cytokines, interleukin 18 seems to play a central role in the inflammatory cascade, leading to development of atherosclerotic disease and the occurrence of ischemic heart disease in uninfected HIV-1 people. Increased levels of interleukin 18 were observed in HIV-1 infected patients.

This review attempts to evaluate the role of interleukin 18 in cardiovascular disease, especially in myocardial infarction, in HIV-1 infection, as well as the relationship between interleukin 18 and atherosclerotic plaque formation.

Two other characteristic aspects in HIV-1 infection, metabolic syndrome and lipodystrophy, will be evaluated in light of activity of interleukin 18. Moreover, the role of platelets and interleukin 18 as an important linkage between chronic inflammation, endothelial dysfunction, and atherogenesis will be highlighted.

Finally, experimental an animal model of rhesus macaques infected with simian immunodeficiency virus clearly demonstrates the involvement of interleukin 18 in myocardial lesions, and that circulating levels of interleukin 18 are important predictors of coronary heart disease.

In conclusion, interleukin 18 may be considered a partner in crime with other factors, including endothelial dysfunction, increased expression and production of adhesion molecules and proinflammatory cytokines in determining cardiovascular disease. **(AIDS Rev. 2010;12:31-9)**

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Key words

Interleukin 18. HIV-1. AIDS. Cardiovascular disease. Atherosclerosis.

Introduction

Cardiovascular disease (CVD) is frequently reported in patients with HIV-1 infection, particularly in those patients in the advanced stage of the disease[1,2]. Before the introduction of effective antiretroviral therapy (ART), retrospective studies and observational analyses reported that cardiac disorders are present in 25-75% of patients with AIDS[3]. Since HIV-1-infected patients develop opportunistic infections, cardiac involvement with pericarditis, endocarditis, and myocarditis is frequently related to opportunistic pathogens[4]. However, among other CVD reported in HIV-1-infected patients, dilated cardiomyopathy and associated symptoms of congestive heart failure are being recognized with increasing frequency[3], as well as ischemia, pulmonary hypertension, and bundle branch block[5]. The ART regimens have significantly modified the course of HIV-1 infection, with

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longer survival rates and improvement of life quality in these patients. On the other hand, the early data have raised concerns that ART is associated with increased coronary artery disease[6]. The largest prospective study of cardiovascular risk with ART, the DAD study, showed that the incidence of myocardial infarction (MI) increased directly with longer exposure to protease inhibitors, but it did not find any relationship between MI and markers of HIV-1 infection such as lower CD4 lymphocyte count and higher levels of plasma HIV RNA[7].

Furthermore, the relative risk for increasing age, male sex, current smoking, elevated cholesterol, low levels of HDL cholesterol, and diabetes mellitus were similar to those observed in studies of HIV-1-uninfected subjects[8,9]. In contrast, a retrospective study showed no relation between the use of combined ART and the hazard of cardiovascular and cerebrovascular events[10]; in addition, Coplan, et al.[11] did not demonstrate a significant increase in MI risk during the first year of protease inhibitor therapy.

Successively, the SMART study showed an increased risk for CVD among patients who interrupted ART when their CD4 lymphocyte count rose above 350 cells/mm^3 [12]. Although ART may be able to contribute to CVD, HIV-1 itself or immunologic factors may play a role in CVD risk. Firstly, HIV-1 may serve as a marker to identify a subgroup of the general population with an altered prevalence of traditional cardiovascular risk factors unrelated to ART; secondly, HIV-1 may affect the pathogenic process that leads to CVD in ways other than via an effect on traditional risk factors, such as through effects on endothelial function or on chronic inflammation; thirdly, HIV-1 may affect the risk of developing a traditional cardiovascular risk factor. Thus, both HIV-1 infection and ART may affect the function of the heart and the vasculature, and endothelial dysfunction is a predominant feature correlated either with HIV-1 itself or with ART. The mechanism of HIV-related endothelial dysfunction is not clear, but may include lipid disorders associated with HIV-1 infection[13], viral protein-related endothelial activation[14], effects of systemic inflammatory cytokine or chemokine dysregulation, or direct HIV-1 infection of the endothelium[15], and vascular smooth muscle cells. Although ART improves endothelial dysfunction, long-term protease inhibitor-based ART may cause severe endothelial dysfunction[16]. It should be noted that HIV-1 infection, as a chronic inflammation, is able to activate and maintain a paramount of immunologic and inflammatory factors, which can significantly contribute to CVD. In fact, Tebas, et al.[17] have suggested that treatment interruptions lead to increased immune cell activation and systemic inflammatory responses along with recrudescent HIV-1 viremia, and this mechanism may explain the increased cardiovascular risk associated with interruption of ART.

In the last decade, several studies have highlighted the role of interleukin 18 (IL-18) in CVD. Interleukin 18 is a new member of the IL-1 family, and induces gamma interferon (IFNγ) production from T helper 1 (Th1) cells in the presence of IL-12[18,19]. Interleukin 18 may act on Th1 cells, natural killer (NK) cells, B-cells, and dendritic cells to produce IFNγ in the presence of IL-12[18-20]. Moreover, a constitutively secreted protein with high affinity binding to IL-18, IL-18BP, has been demonstrated and it is highly expressed in spleen and intestinal tract, both of which are immunologically active tissues[21,22]. Elevated concentrations of IFNγ stimulate more IL-18BP in an attempt to reduce IL-18-mediated IFNγ production[23].

We firstly observed increased circulating levels of IL-18 in symptomatic HIV-1-infected patients as well as in those with AIDS[24], and this cytokine, during the different stages of the disease, has shown proviral activity in both maintaining and worsening HIV-1 infection[25]. In addition, ART induces a marked decline of serum levels of IL-18, and virologic treatment failure was associated with persistently raised levels of IL-18[24,26,27]. However, previous *in vitro* studies showed that IL-18 stimulated HIV-1 replication in the chronically infected T-cell line[28]. Senpuku, et al.[29] have shown that nonobese diabetic-severe combined immunodeficiency mice infected with HIV and successively treated with IL-18 had a higher viral replication, indicating that IL-18 may support HIV-1 infection. It should be noted that human heart tissue contains preformed IL-18 in macrophages and endothelial cells[30], and in the last decade IL-18 has become an important cytokine in myocardial ischemia reperfusion injury, a model of acute infarction, where it functions to decrease the contractile force of the heart[30].

Pathogenic role of interleukin 18 in cardiovascular disease

Several cardiac manifestations show a significant increase of IL-18 serum levels. Patients with congestive heart failure showed increased serum levels of IL-18[31]. Moreover, plasma IL-18 concentrations were significantly elevated in patients with acute myocardial infarction, and the peak IL-18 concentration in these

patients correlated with specific serum markers of acute myocardial infarction[32]. Patients with stable and unstable angina exhibited higher serum levels of IL-18 in comparison to control subjects, and levels of IL-18 did not differ significantly between patients with stable and unstable angina[33]. Plasma concentrations of IL-18 are also increased in patients with acute coronary syndromes with or without myocardial necrosis[34]. Moreover, patients with documented coronary disease and subsequent fatal cardiovascular events exhibit high serum levels of IL-18 compared to those with a low level of IL-18[35]. In an *in vitro* study in the human myocardium, IL-18 is upregulated following ischemia and contributes to postischemic myocardial dysfunction[30]. Animal studies have also demonstrated increased levels of IL-18 mRNA and plasma IL-18 after myocardial infarction[36], and that treatment with IL-18BP improved postischemic myocardial dysfunction through attenuating myocardial levels of IL-18 in a murine model[30].

Thus, several cellular and molecular mechanisms concerning IL-18-induced myocardial injury can be postulated, including stimulation of inflammatory response, increase of apoptotic activity, and changes in intracellular calcium.

Firstly, IL-18 is able to stimulate production of IFNγ from infiltrated neutrophils, resident macrophages, and endothelial cells in the heart, and this provokes myocardial inflammation and depression of myocardial contractility[37]. In addition, IL-18 is able to stimulate production of other cytokines, including IL-6, IL-1, and tumor necrosis factor (TNF), leading to further alter myocardial function[38]. Worsening of myocardial inflammation is also provoked by IL-18-induced expression of vascular adhesion molecule 1 and intracellular adhesion molecule 1, two chemokines that recruit leukocytes into the injured myocardium[38]. Interleukin 18 also increases the activity of cytotoxic T lymphocytes[39], and all these factors contribute to mediate myocardial dysfunction.

Secondly, IL-18 is able to stimulate myocardial apoptosis with loss of cardiomyocytes. This activity may be an indirect effect through induction of several cytokines, including TNFα, IL-1β, and IL-6, or a direct effect through upregulation of Fas-ligand in NK cells and TH1 cells[40,41]. Moreover, antiapoptotic proteins, including Bcl-2 and Bcl-Xl, are decreased by IL-18, whereas proapoptotic protein Bcl-Xs is upregulated by IL-18[42].

Thirdly, IL-18 is also able to affect myocardial contractile function through changes in intracellular calcium. Elevated IL-18 levels have been correlated with decreased left ventricular ejection fraction in patients with acute coronary artery disease[34]. In addition, administration of IL-18 in mice provokes increased calcium in cardiomyocytes that is associated with depressed myocardial contractility and relaxation[43], and exposure of myocardium to IL-18 reduces the responsiveness of the myofilaments to calcium[43].

All these findings suggest that IL-18 may able to provoke inflammation, apoptotic activity, and alteration of intracellular calcium homeostasis, and this leads to myocardial injury with persistent myocardial dysfunction.

Interleukin 18 atherosclerosis and HIV-1 infection

Patients with HIV-1 infection have higher rates of atherosclerosis, and the progression is faster than in uninfected individuals[44,45]. Atherosclerotic cardiovascular disease, a leading cause of morbidity and mortality in the general population, is an increasing cause for concern for HIV-1-infected patients as well[46].

Since atherosclerosis is a chronic inflammatory process, several inflammatory factors, including atherogenic lipoproteins, inflammatory cells (macrophage-derived foam cells and T-cells), platelets, and several inflammatory cytokines are involved[46]. In fact, HIV-1-infected patients are prone to continuous inflammatory stimuli, which may trigger a cytokine imbalance that can influence the development of atherosclerosis[47].

As shown in figure 1, atherosclerosis is a specific form of chronic inflammatory process, resulting from interaction between plasma lipoproteins, monocyte/macrophage, T lymphocytes, endothelial cells, and smooth muscle cells and the extracellular matrix of the arterial wall[48]. In addition, HIV-1 infection could represent a risk factor for the development of endothelial damage, inasmuch as HIV-1 itself can activate the endothelium directly or by a leukocyte-mediated inflammatory cascade through increase of adhesion mediators[49,50]. Elevation of atherogenic lipoproteins may lead to the deposition in the intima, and macrophages may take up deposited atherogenic lipoproteins and be transformed into foam cells. It should be noted that atherosclerotic plaque contains inflammatory and immune cells, mainly macrophages and numerous T lymphocytes, as well as endothelial cells, smooth muscle cells, extracellular matrix lipids, and

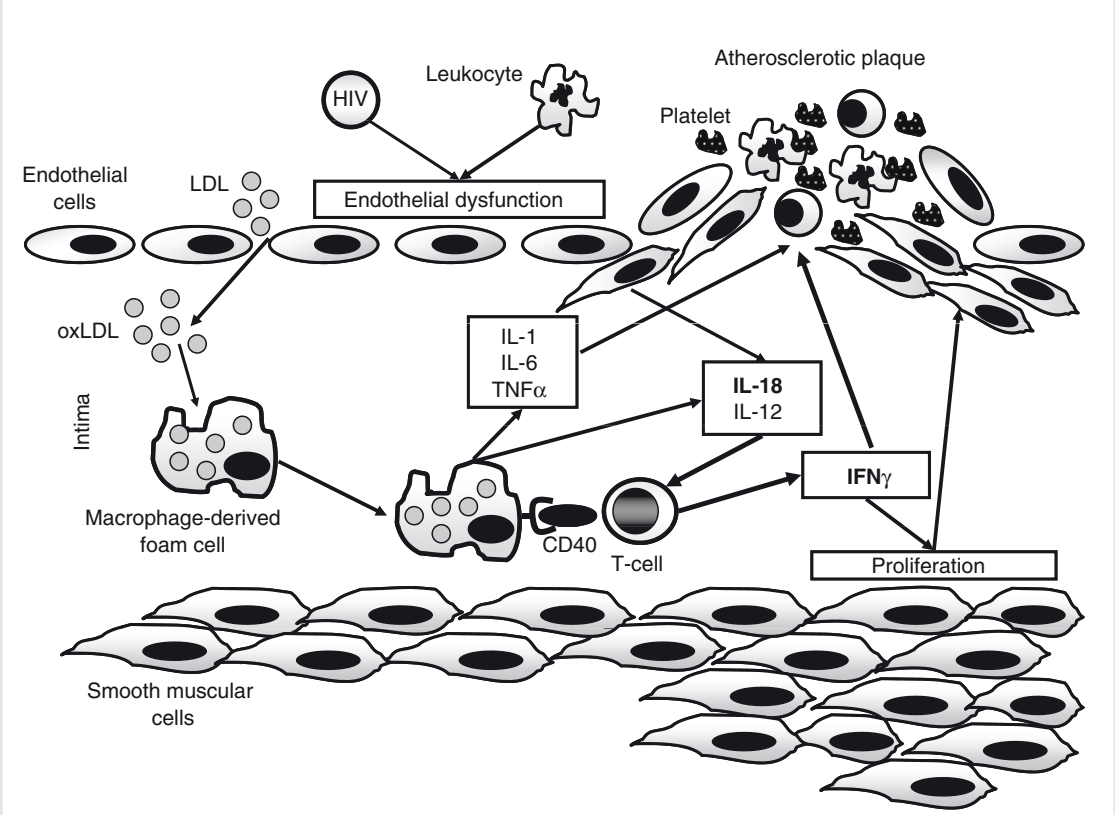

Figure 1. *Proposed mechanisms of interactions among HIV-1, endothelial cells, macrophage-derived foam cells, proinflammatory cytokines, inflammatory cells (neutrophils, T-cells, platelets), and smooth muscle cells in formation of atherosclerotic plaque. LDL: low density lipoprotein; OxLDL: oxidized low-density lipoprotein; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor.*

platelets[51] (Fig. 1). Macrophages and foam cells migrated into the subendothelial space are responsible for producing proinflammatory cytokines, including IL-1, IL-6, and TNFα, and more important IL-12 and IL-18. Atherosclerosis is a Th1 cell-driven disease, since human plaques contain cells producing IFNγ, IL-12, IL-15, IL-18, and TNFα, but few cells producing Th2-type cytokine IL-4[52]. Cell components of atheroma, including macrophages, endothelial cells, and smooth muscle cells, express receptor subunits of IL-18[53]. In addition, IL-18 along with IL-12 is an inducer and regulator of the expression of IFNγ, a major proinflammatory cytokine during atherogenesis[18], and IL-18 induces IFNγ expression, not only in T-cells, but also in smooth muscle cells and macrophages, thus activating the proinflammatory pathway operating during atherogenesis[18,53]. Furthermore, Gerdes, et al.[53] have found that vascular macrophages and smooth muscle cells may secrete IFNγ under the stimulation of IL-18, and these cells can express receptors of IL-18 as well. As shown in figure 1, platelets also play a central role in the biology of atherosclerosis by producing inflammatory mediators such as CD40 ligand and platelet-derived growth factor, as well as directing leukocyte incorporation into plaques through platelet-mediated leukocyte adhesion[54].

Several lines of evidence support a major proatherogenic role for IL-18. Table 1 shows several experimental studies *in vivo* concerning IL-18 activity in experimental models utilizing apolipoprotein E-knockout mice, as well as *in vitro* studies using vascular endothelial cells and smooth muscle cells.

Expression of IL-18 and its receptor subunits is increased in atherosclerotic arteries compared with normal arterial segments[53]. It has been demonstrated that IL-18 accelerates atherogenesis in IL-18-deficient apolipoprotein E-knockout mice[55], and that inhibition of IL-18 signaling decreases atherosclerotic plaque

Table 1. Proatherogenic effect of interleukin 18 *in vitro* and *in vivo* experimental studies

Author (Reference)	Mechanism of action
Gerdes, et al.[53]	Inflammatory response in vascular endothelial cells and smooth muscle cells
Elhage, et al.[55]	Reduced atherosclerosis in IL-18 deficient mice
Mallat, et al.[56]	Modulation of atherosclerotic plaque development
Tenger, et al.[57]	Enhancement and acceleration of atherosclerosis
Whitmann, et al.[58]	Enhancement of atherosclerosis in deficient apolipoprotein E mice

formation[56], whereas administration of exogenous IL-18 provokes atherogenesis and more fatty than fibrous lesions[57]. This proatherogenic effect of IL-18 can be abolished in the absence of IFNγ[58], suggesting that worsening of atherosclerosis from IL-18 is strictly dependent on production of IFNγ.

In an experimental model of simian immunodeficiency virus-infected macaques, atherogenic diet increased plasma levels of IL-18, and the IL-18 levels were predictive of short survival[59]. Moreover, after infection, plasma IL-18 levels correlated closely with viral load[59].

All these *in vitro* and *in vivo* studies on the atherogenic role of IL-18 were confirmed in clinical studies, which demonstrated increased IL-18 levels in patients with stable and unstable angina, in patients with myocardial infarction, and in those with coronary artery disease[34,33,32,60]. Moreover, it has been demonstrated that there is a strong association between IL-18 and several cardiovascular risk factors, particularly those linked with the metabolic syndrome (MS)[61].

Interleukin 18, metabolic syndrome and HIV-1 infection

The metabolic syndrome is characterized by abdominal obesity, hypertriglyceridemia, a low high-density lipoprotein cholesterol level, hypertension, and insulin resistance[62]. This syndrome is directly associated with a high incidence of CVD, and specifically atherosclerosis[63]. Several abnormalities found in HIV-1-infected patients with lipodystrophy overlap with the components of MS, and it has been observed that there is an elevated risk of premature atherosclerosis and adverse cardiovascular events among HIV-1 infected patients[13,64]. There are several evidences that IL-18 levels may be linked with metabolic risk factors. Hung, et al.[61] have found that IL-18 concentrations were specifically correlated with a range of metabolic risk traits, including body mass index, waist circumference, triglycerides, high density lipoprotein, blood pressure, and fasting insulin levels, and this finding with IL-18 further enhances the argument that inflammation and activated immunity, through cytokine response, are involved in the cluster of metabolic and cardiovascular risk factors. Levels of IL-18 are known to be elevated in patients with obesity, which represent a key risk factor for the development of CVD[65-68], and insulin resistance, and that weight loss also caused a decrease of systemic IL-18 concentrations[65,66].

Skurk, et al.[69] demonstrated that human adipocytes release IL-18 spontaneously, and there is upregulation of IL-18 release in adipocyte cultures from obese compared with lean or overweight control subjects. In contrast, it has been recently shown that IL-18 improves experimental hyperphagia[70], but a successive study showed a defective response to IL-18 stimulation correlated with decreased expression of IL-18 receptor subunits[71]. This IL-18 resistance may explain the association of obesity and diabetes with increased concentrations of IL-18, similar to hyperinsulinemia and hyperleptinemia. Straczkowski, et al.[72] have observed that increased serum levels of IL-18 were associated with low serum levels of adiponectin in patients with obesity, and they postulated that IL-18 might be the factor inhibiting adiponectin secretion from adipose tissue[72]. The HIV-1-associated lipodystrophy has characteristics in common with MS: hypertriglyceridemia, hypercholesterolemia, increased lipolysis, and insulin resistance. It has been demonstrated that HIV-1-infected patients with lipodystrophy (lipoatrophy with or without central fat accumulation) show elevated serum levels of IL-18, and IL-18 is mechanistically linked to the low total limb fat mass[73,74]. In addition, in HIV-1-infected patients with hypertriglyceridemia, a positive correlation was found between serum ghrelin, adiponectin, and IL-18 levels, and these molecules might be involved in the pathogenesis of metabolic disorders in HIV-1 infection[75].

Thus, marked abnormalities in inflammatory markers, including IL-18 and adiponectin, may represent reliable biomarkers of MS in HIV-1-infected patients with lipodystrophy.

Interleukin 18 and platelets: Bridging HIV-1 infection and cardiovascular disease

Platelets represent an important linkage between chronic inflammation, endothelial dysfunction, and atherogenesis, and this is becoming particularly true for HIV-1 infection, inasmuch as platelet adhesion, inflammatory cytokines, adhesion molecules, and inflammatory cells may contribute to endothelial damage, which leads to formation of atherosclerotic plaque[76].

Figure 2 illustrates the interaction of HIV-1 with platelets in inducing chronic inflammatory processes at the vascular wall that result in the development of atherosclerotic lesions and atherothrombosis.

The initial loose contact between circulating platelets and vascular endothelium (platelet rolling) is mediated by P-selectin, which is present on both platelets and endothelial cells[77]. Successively, a firm adhesion between the platelet and the endothelium is achieved by integrins[78] (Fig. 2 A). The rolling and firm adhesion of platelets to endothelium plays an important role in the initiation and progression of vascular inflammation, combined with binding of platelets with HIV-1 through the fibronectin receptor present on their surface[79] (Fig. 2 A). In addition, platelets may be considered as carriers for persistent replication and systemic spread of HIV-1[79]. During the adhesion process and binding to HIV-1, platelets become activated and release huge amounts of potent inflammatory and mitogenic substances, including chemokines (RANTES, platelet factor 4), growth factors (platelet-derived growth factor, transforming growth factor beta, epidermal growth factor), and cytokine-like factors (IL-1β, CD40 ligand, beta-thromboglobulin), and IL-18[80] (Fig. 2 B). It should be noted that IL-18 along with HIV-1 are able to activate platelets. In fact, Ahmad, et al.[81] found that human platelets contain abundant amounts of IL-18, which they release upon activation; in addition, they observed enhanced platelet activation by IL-18 in HIV-1-infected patients (Fig. 2 B).

All these events lead to chronic inflammation of endothelial cells and this represents a crucial aspect of endothelial dysfunction during the symptomatic and advanced stages of HIV-1 infection.

HIV-1 enhances chemokine release and upregulates endothelial molecules and through platelet adherence to the endothelium[80] (Fig. 2 C).

Finally, all these processes lead to formation of atherosclerotic plaque. As shown in figure 2 D, in this stage activated platelets play an important role in the formation of aggregates with inflammatory cells, including T-cells, neutrophils, and monocytes. In fact, circulating activated platelets and platelet-neutrophil/monocyte aggregates promote formation of atherosclerotic lesions[82]. Lymphocyte-conjugated platelets enhance lymphocyte adhesion on the endothelium, and platelet-lymphocyte aggregates are critical in the formation and exacerbation of atherosclerotic plaque[83-85]. Furthermore, active proliferation of smooth muscle cells along with foam cells and platelet-inflammatory cell aggregates are critical for the formation and exacerbation of atherosclerotic plaque (Fig. 2 D).

Summary and concluding remarks

In this review, we have shown a prominent role for IL-18 in atherosclerosis and its activity on several inflammatory cells, including monocytes/macrophages, platelets, T-cells, and particularly on the endothelial cells. Besides, in the last years, several experimental and clinical studies have highlighted the role of IL-18 either in HIV-1-related lipodystrophy and MS or its likely effect on myocardial function in HIV-1-infected patients. In fact, pathogenic mechanisms of CVD and, in particular ischemic heart disease, in HIV-1 infection are essentially based on endothelial dysfunction, on abnormal and persistent inflammatory cytokine response, and on inflammatory cells, including macrophages/foam cells, T-cells, and platelets. Thus, all these events in the chronic inflammation of HIV-1 infection are responsible for atherosclerosis.

However, it should be noted that a direct pathogenic link between IL-18 and myocardial lesions in HIV-1 infection has not yet been demonstrated, inasmuch as previous studies have evaluated atherosclerosis in chronic HIV-1 infection. Evaluation of immune and pathologic changes in early stages of HIV-1 infection is crucial to understand early immune response and pathologic changes leading to atherosclerosis. Unfortunately, this approach is not feasible in HIV-1-infected patients since most of them are not diagnosed until an indeterminate length of time after primary infection.

However, in the last two years, Yearley, et al.[86,87] have investigated, in two studies, myocardial lesions and progression of atherosclerosis in an experimental model of macaques infected with pathogenic simian immunodeficiency virus (SIV-strain mac 251).

In the first study, Yearley, et al.[86] found in the SIV-infected group a significant increase of plasma levels of IL-18 relative to baseline by day 14, correlated with the occurrence of peak viremia; in addition, increased

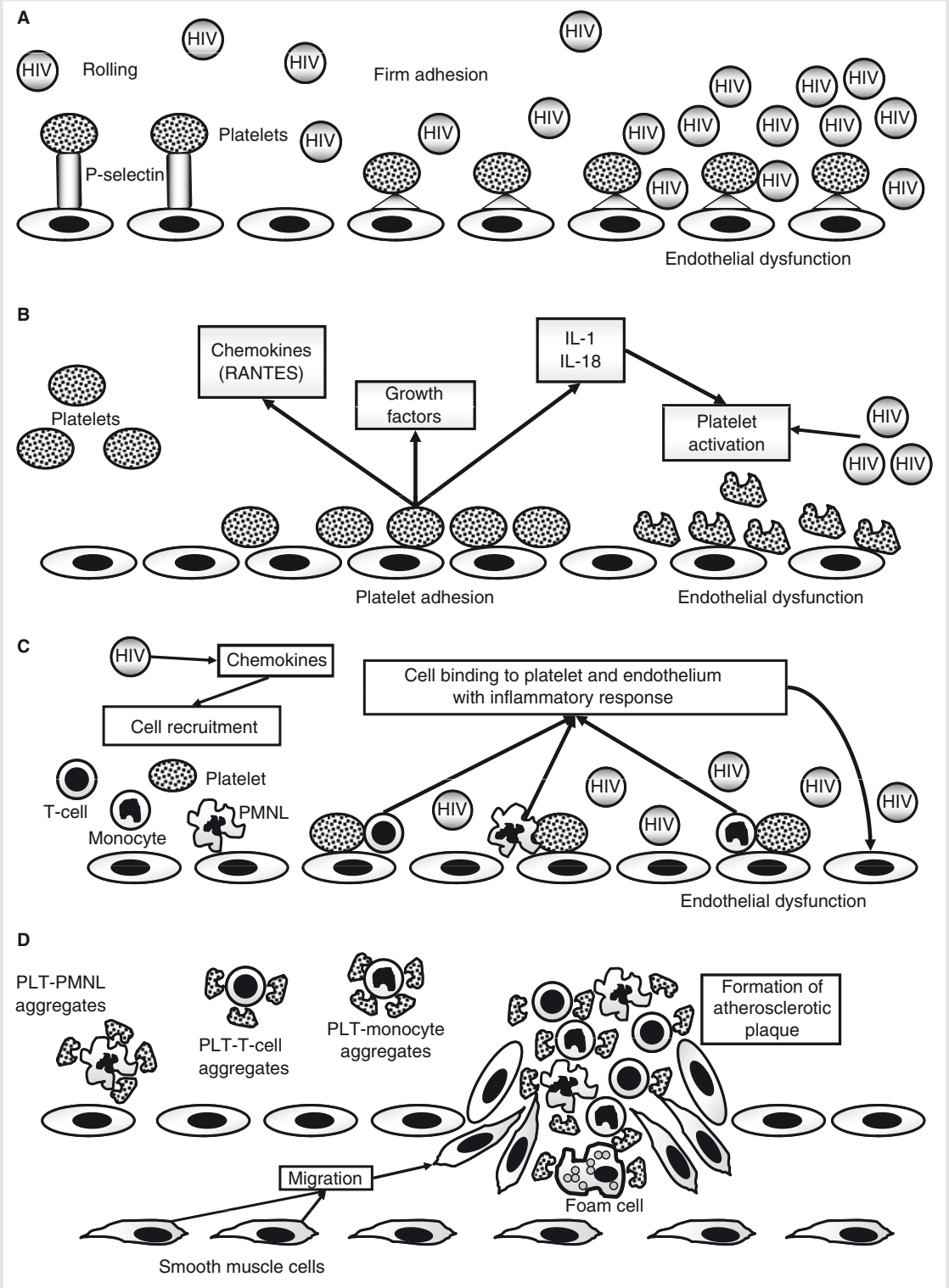

Figure 2. A: *Proposed mechanisms of interactions of HIV-1, endothelial cells, with platelets for their rolling and firm adhesion to endothelium.* **B:** *Interactions of platelets with chemokines, growth factor and IL-18 in platelet activation and subsequent endothelial dysfunction.* **C:** *Cell intravascular recruitment by HIV-1, and cell binding (neutrophils, T-cells and monocytes) to platelets with subsequent endothelial dysfunction.* **D:** *Formation platelet-T cell aggregates, platelet-neutrophil aggregates and monocyte-platelet aggregates, and subsequent formation of atherosclerotic plaque. IL: interleukin; PMNL: polymorphonuclear leukocytes; PLT: platelet.*

levels of IL-18 were correlated significantly with increased left ventricular end-diastolic diameter at day 35. These investigators have shown that the degree of immune response activity around the period of peak viremia may directly contribute to the extent of subsequent myocardial lesions, suggesting that immune activation, expressed as increased production of proinflammatory cytokines, may also play an important role in myocardial end-organ damage.

In a more recent study, the same investigators, in the SIV-infected macaques maintained on an atherogenic diet for six months, observed a significant correlation between basal plasma levels of IL-18 and atherosclerotic lesion severity at necroscopy[87]. In addition, IL-18 plasma levels correlated with levels of T-cell and macrophage foam cell infiltration, and extent of vascular lipid accumulation. It also should be noted that baseline circulating IL-18 levels have been identified as important predictors of stable and unstable angina, and more generally of coronary heart disease in uninfected HIV-1 people[35,60,88], as predictors of accelerated SIV disease in macaques on a diet high in saturated fat and cholesterol[59], and as predictors of future systolic dysfunction in a rhesus model of HIV-associated cardiomyopathy[86].

In summary, this review highlights and confirms the more prominent and crucial role of IL-18 in CVD, either in uninfected HIV-1 subjects or in experimental animal models infected with SIV.

It is interesting to note that in the SMART study[12], the risk of CVD was higher among HIV-1-infected patients who went off ART, a surprising finding in light of the known lipid-raising effect of several antiretrovirals. In fact, a persistently high viral load in the absence of treatment leads to increased and chronic activation of inflammatory markers, including IL-18 and other proinflammatory cytokines, that may further increase the risk of damage to the cardiovascular system. Thus, the link between HIV-1 infection and atherosclerosis, clinically expressed as CVD, is probably related to endothelial dysfunction, increased expression and production of adhesion molecules and proinflammatory cytokines, particularly IL-18, and activation of platelets.

In conclusion, growing experimental and clinical results show that proinflammatory cytokine IL-18, along with other proinflammatory cytokines, may play a predominant and causative role in determining myocardial ischemic dysfunction, and IL-18 can be considered a partner in crime along with other immunological and clinical factors in determining CVD in HIV-1-infected patients.

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