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Endothelial Cell Dysfunction in HIV-1 Infection

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Abstract

Human immunodeficiency virus type 1 (HIV-1) promotes a generalized immune activation that alters the physiology of cells that are not sensitive to viral infection. Endothelial cells (ECs) display heavy dysfunctions in HIV-1-seropositive (HIV⁺) patients that persist even in patients under successful combined antiretroviral therapy (cART). In vivo studies failed to demonstrate the presence of replicating virus in ECs suggesting that a direct role of the virus in vascular dysfunction is unlikely. This finding paves the way to the hypothesis of a key role of molecules released in the microenvironment by HIV-1-infected cells in sustaining aberrant EC function. Here we review the current understanding regarding the contribution of HIV-1 infection to vascular dysfunction. In particular, we argue that different HIV-1 proteins may play a key role in driving and sustaining inflammation and EC dysregulation, thus underlining the need to target them for therapeutic benefit.

Keywords: HIV-1, viral proteins, endothelial cells, vascular dysfunction, inflammation

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) infection is highly pathogenic since it stimulates a generalized immune activation involving not only the main targets of HIV-1 infection, such as CD4⁺ T cells and monocytes/macrophages, but also cells that are not sensitive to viral infection.

Endothelial cells (ECs) are not fully permissive to HIV-1 infection, and there are no in vivo evidences that demonstrate the presence of replicating virus in ECs. Nowadays, the number of HIV-1-seropositive (HIV⁺) patients that exhibit EC dysfunction is increasing vertiginously. In this chapter, the actual knowledges of how HIV-1 can directly and/or indirectly contribute to vascular dysfunction are reviewed. In particular, we underline the emerging role played by

some structural and regulatory HIV-1 proteins released in the microenvironment by infected cells in driving inflammation and EC dysregulation. This finding highlights the need to target these viral proteins for therapeutic benefit.

2. Endothelial dysfunction during HIV-1 infection

Chronic inflammation contributes to many leading causes of death, and in particular cardiovascular events have emerged as a clinically significant issue and have become the matter of several studies. HIV-1 infection is characterized by altered immune responses leading to a generalized chronic inflammation and, in particular, to a pro-inflammatory status in the vascular endothelium fostering the development of cardiovascular diseases [1]. A strong correlation between high plasma HIV-1 RNA levels and signs of endothelial dysfunction is known [2], and subclinical signs of atherosclerosis have been found in asymptomatic HIV⁺ young men with long-standing HIV-1 disease [3]. As the efficacy of combined antiretroviral therapy (cART) improves and patients live longer, the prevalence of cardiovascular diseases is increasing in HIV⁺ individuals [4, 5]. Moreover, many antiretroviral drugs, particularly HIV-1 protease inhibitors, can cause dyslipidemia, thus contributing to the increased risk for endothelial dysfunction. The high risk of endothelial dysfunction persists even in new-generation antiretroviral drugs era, despite the fact that several adverse metabolic effects (e.g., insulin resistance, dyslipidemia, and hypertension) are abolished [6]. In light of these considerations, the following paragraphs consider three essential factors in the development and pathogenesis of endothelial dysfunction during the natural course of HIV-1 infection: (a) the ability of HIV-1 to promote inflammation, (b) the HIV-mediated damage of endothelium, and (c) the capability of HIV-1 structural and regulatory proteins of affecting EC function.

2.1. HIV-1 and inflammatory microenvironment

Chronic activation of the immune system is a peculiar feature of HIV-1 infection. Persistent activation of immune cells is known to gain an elevated pro-inflammatory cytokine/chemokine release contributing to the development of a chronically inflamed microenvironment. HIV-1 virus cycle is dominated by a local replication at the transmission site and in local lymphoid tissues and then dissemination. Virus expansion is associated with a dramatic depletion of memory CD4⁺ T cells, particularly from gut-associated lymphoid tissues and with increased plasma levels of pro-inflammatory cytokines and chemokines. During the early phase of infection, a pro-inflammatory cytokine storm contributes to the control of viral replication but also to the early immunopathology of the infection and to the associated long-term consequences. Many cell types contribute to the release of different pro-inflammatory cytokines and chemokines during HIV-1 infection [7] such as interferon (IFN)- α , tumor necrosis factor (TNF)- α , INF- γ , interleukin (IL)-1 β , IL-10, interferon gamma-induced protein (IP)-10, IL-15, IL-8, IL-6, IL-18, and monocyte chemoattractant protein (MCP)-1 [8, 9]. Antiretroviral therapy usually controls and even abolishes HIV-1 replication, but does not completely recover immune dysfunction. Therefore, immune alteration and inflammation are common features of HIV⁺ patients even under successful cART.

2.2. Role of inflammatory cytokines and chemokines in the HIV-1-triggered endothelial dysfunction

Endothelial dysfunction and vascular diseases such as atherosclerosis and arterial damage are predominantly enhanced during a systemic chronic inflammatory status. Elevated levels of IL-6 have been associated with carotid atherosclerosis and progressive stenosis of the carotid artery, thereby upregulating the lipid uptake in macrophages and inhibiting the activity of lipoprotein lipase [10]. Increased carotid intima-media thickness (IMT) and hypertension are common features of patients with increased plasma levels of IL-18 [11], whereas TNF- α has a key role in promoting atherosclerosis, myocardial ischemia/reperfusion, and heart failure via several mechanisms: increased cholesterol uptake and foam cell formation in macrophages, augmented leukocyte transmigration in subendothelial structures, and increased proliferation and migration of vascular smooth muscle cells [12].

HIV-1 infection generates a systemic chronic inflammatory disorder as a result of continuous alteration of the immune response, contributing to dyslipidemia, EC dysfunction, vascular smooth muscle cell proliferation and migration, and, ultimately, the atherosclerotic plaque formation. The virus itself promotes the release of IL-6, IL-18, and TNF- α , together with IFN- γ , IL-1 β , IL-10, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and macrophage colony-stimulating factor (M-CSF) by T cells and monocytes [13].

Liver-synthesized C-reactive protein (CRP) is a member of the pentraxin family factors and is considered a marker for coronary vascular disease and endothelial damage. CRP plasma levels are significantly upregulated in HIV⁺ patients and inversely correlated with CD4⁺ T lymphocyte count [14], and elevated CRP levels have been associated with an increased risk of myocardial infarction in HIV⁺ patients [15]. It is noteworthy that increased levels of IL-6, IL-1, and TNF- α induce CRP, which in turn is able to activate pro-inflammatory cytokines such as IL-6 and M-CSF via a positive feedback loop.

The levels of cell adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) are raised during HIV-1 infection, thus contributing to trans-endothelial migration of immune cells [16].

HIV-1 causes a continuous recruitment of monocytes that migrate across the endothelial barrier in blood vessels, differentiate into macrophages, and produce pro-inflammatory cytokines, thus determining the progressive damage of vessel structures. Furthermore, HIV-1 replicates in macrophages and induces activation and synthesis of several pro-inflammatory cytokines that in turn induce endothelial activation and leukocyte adhesion generating a positive feedback [17].

An important alteration in lipid metabolism is evident in more than 50% of HIV⁺ patients. It likely relies on the upregulation of hepatic fatty acid synthesis and very low-density lipoprotein (VLDL) production, usually triggered by inflammatory cytokines as IFN- γ , TNF- α , and IL-1 β [18]. At the same time, the continuous trans-endothelial migration of immune cells and their inhibited reverse transport determines the localization of monocytes inside the vessel wall and promotes the formation of foam cells, the fat-laden macrophages that are implicated in the buildup of an atheromatous plaque [17].

Monocytes, depending on the cytokine/chemokine stimulation, may differentiate into M1 macrophages, which promote inflammation or into M2 macrophages, which are inflammatory resolving cells [19]. In particular, IFN- γ and IL-1 β drive monocytes to acquire an M1 profile, whereas IL-4 and IL-13 generate M2 macrophages. HIV-1, by infecting macrophages, polarizes these cells toward the M1 phenotype [20]. This leads to the imbalance of the M1/M2 ratio, a condition necessary for sustaining endothelial dysfunction [21].

Endothelin-1 (ET-1) is a potent vasoconstrictor that promotes migration and proliferation of smooth muscle cells. HIV-1-triggered secretion of ET-1 promotes a reduction of vascular nitric oxide (NO) production by ECs with the consequent proliferation and migration of smooth muscle cells leading to arterial vasoconstriction.

Altogether, these findings suggest that HIV-1 produces a general inflammatory microenvironment that contributes to dyslipidemia, EC dysfunction, chemotaxis, and vascular smooth muscle cell proliferation and migration. All these conditions are likely to foster endothelial degeneration and atherosclerotic plaque formation (**Figure 1**).

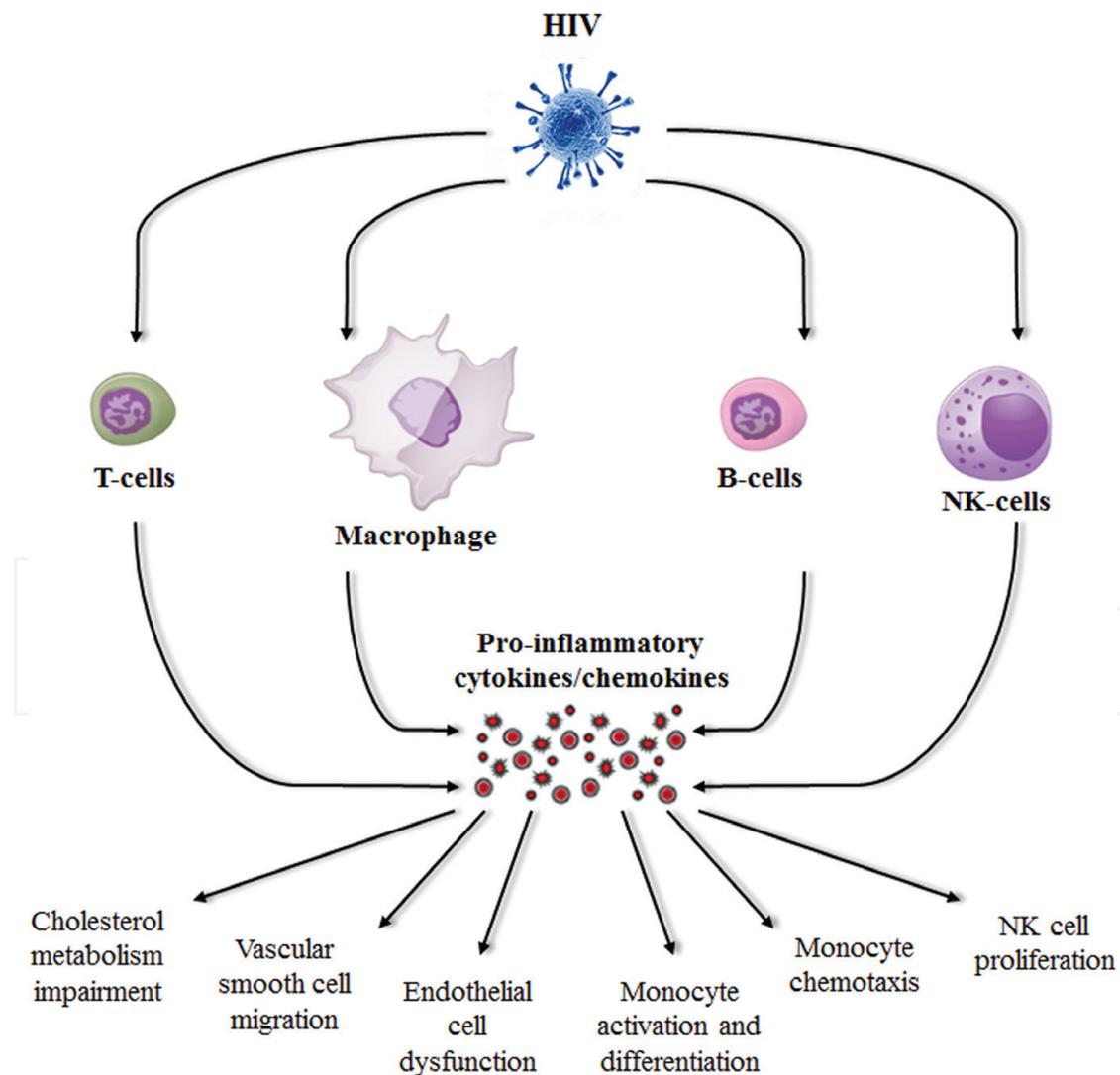


Figure 1. HIV-1 capability to promote inflammation, dyslipidemia, and endothelial dysfunction through the activation of different immune cells such as T and B cells, macrophages, and natural killer cells (NK cells).

2.3. HIV-1-triggered damage of ECs

HIV-1 is not an endothelium-tropic virus. It displays a narrow tropism predominantly determined by the cell surface receptors required for HIV-1 infection. CD4 and co-receptors are usually essential for HIV-1 to infect cells efficiently. The chemokine (C-C motif) receptor type 5 (CCR5) is the main co-receptor used *in vivo*, but variants that use another co-receptor, namely, chemokine (C-X-C motif) receptor type 4 (CXCR4), evolve during disease. *In vitro*, more than a dozen different co-receptors have been identified that support infection of cell lines by different HIV-1 strains. Moreover, HIV-1 particles interact with a range of cell surface receptors via interactions of its envelope glycoprotein gp120 with glycolipid galactocerebroside (gal)-C and its sulfated derivative.

HIV-1 capability to infect ECs *in vitro* depends on the tissue source of ECs and on their functional status. Microvascular ECs from the brain, kidney glomeruli, hepatic sinusoid, and bone marrow may be infected by HIV-1 in the absence of cytolysis [22, 23]. HIV-1 infection of brain ECs has been largely studied for its relevance in neurological diseases. T cell tropic but not brain-derived macrophage tropic HIV-1 strains selectively infect the brain endothelium *in vitro*, suggesting that T cell tropism may be important for HIV-1 entry through the blood-brain barrier [22] and spreading in the central nervous system [24]. However, it is important to underline that *in vivo* studies do not support the presence of replicating virus in ECs. Even if HIV-1 infection of ECs cannot be completely ruled out, this may suggest an indirect action of molecules released in the microenvironment by HIV-1-infected cells at the base of the mechanism for vascular dysfunction.

In the pathophysiology of cardiovascular disease, the damage of ECs assessed by responses to altered blood flow (e.g., flow-mediated dilatation) and differences in the levels of EC specific molecules released in the blood (e.g., von Willebrand factor) represent a hallmark. The equilibrium between the mechanisms of vascular damage and repair plays a crucial role during homeostasis of vascular integrity. Following a blood vessel injury, high levels of circulating ECs (cECs) and microvesicles are released from endothelium, and the reinstatement of the vascular integrity mainly implies activity of endothelial progenitor cells (EPCs), plaque neo-vascularization, and reverse cholesterol transport [25]. EPCs are key determinants of endothelial dysfunction and show a high predictive value of early vascular disease. Interestingly, all vascular repair mechanisms are impaired in HIV⁺ individuals who have lower EPC levels than HIV-1-seronegative subjects [26]. Decrease in the number of EPCs is attributed to HIV-1, which seems to be able to infect these cells because of their chemokine receptor CCR5 and CXCR4 expressions.

Along with reduced EPC levels, HIV⁺ individuals show high plasma levels of EC-derived microvesicles also known as microparticles that are small membranous structures released from ECs during apoptosis, which impair the restoration of physiological conditions and sustain endothelial dysfunction [27]. HIV⁺ patients also exhibit high plasma concentrations of high sensitivity C-reactive protein (hsCRP), IL-6, TNF- α , D-dimer, fibrinogen, soluble ICAM, and VCAM, suggesting endothelial activation and damage. These molecules are also responsible for an increased interaction of infected monocytes with ECs, thereby disrupting the integrity of the EC monolayer and promoting extravasation of HIV-1-infected cells into peripheral tissues and viral dissemination [28].

2.4. Role of HIV-1 proteins in the pathogenesis of endothelial dysfunction

The HIV-1 genome encodes a total of three structural proteins, two envelope proteins, three enzymes, and six accessory proteins. HIV-1 has designed its structural and regulatory/accessory proteins to better adapt to the human host and to promote virus replication and transmission. Among the many functions in the virus life cycle, a major role played by different HIV-1 proteins in directly driving inflammation and EC dysregulation is strengthening (Figure 2), thus highlighting the need to target them for therapeutic benefit.

2.5. HIV-1 structural proteins

The HIV-1 gp120 is the key protein for viral entry by binding to the CD4 receptor and to the co-receptor CCR5 or CXCR4. The HIV-1 matrix protein p17 (p17) is a myristoylated protein that exerts many important and crucial functions during the virus cell cycle. It contributes to nuclear localization of the pre-integration complex after HIV-1 entry and promotes virus maturation and assembly [29]. In addition to its key role in the virus life cycle, p17 exerts a chemokine-like activity by binding to the chemokine receptor CXCR1 and CXCR2 and mimics some of the biological activities of IL-8, the CXCR1 and CXCR2 natural ligand.

Binding of gp120 and p17 to their receptors and/or co-receptors alters the biological activity of different cells. Extracellularly, p17 alters immune responses by activating different immune cells such as CD4⁺ T cells, CD8⁺ T cells, NK cells, plasmacytoid dendritic cells, monocytes, and B cells and contributing to the production and release of pro-inflammatory molecules and to the development of an inflammatory microenvironment [30–32]. Furthermore, p17 stimulates the rapid adhesion and chemotaxis of monocytes and B cells through activation of the Rho/

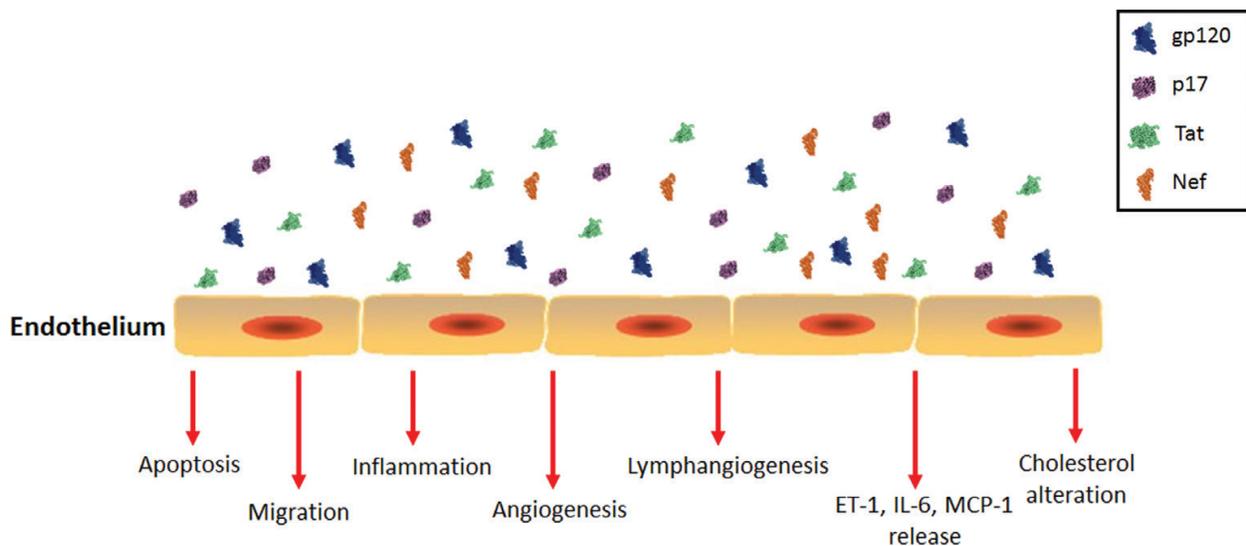


Figure 2. Role of HIV-1 structural and regulatory proteins in the pathogenesis of inflammation and endothelial cell (EC) dysfunction: endothelin-1 (ET-1), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), HIV-1 glycoprotein-120 (gp120), HIV-1 matrix protein (p17), HIV-1 transactivator of transcription (Tat), and HIV-1 negative regulatory factor (Nef).

ROCK signaling pathway [33], suggesting that p17 may recruit activated monocytes and B cells in different tissues and organs to participate and/or sustain inflammatory processes.

On the other hand, gp120 is known to induce dysfunction of T cells, macrophages, cardiomyocytes, ECs, and central nervous system cells, when expressed on the viral particle, on the surface of infected cells, or as a viral-free soluble protein [34].

Endothelial dysfunction mediated by these two HIV-1 structural proteins results to occur through different mechanisms: gp120 is considered a direct and indirect proapoptotic factor favoring EC death, whereas p17 is a potent angiogenic and lymphangiogenic factor.

EC death by gp120 is mediated by its interaction with CXCR4 expressed on the endothelial cell surface that triggers different downstream effects, as activation of the CXCR4-dependent caspase and the mitogen-activated protein kinase (MAPK), or through protein kinase C (PKC) activation [35]. The indirect mechanism of gp120 apoptosis is based on the increased secretion of ET-1 [36, 37], inhibition of NO synthase [38], and a higher surface expression of endothelial monocyte-activating polypeptide II (EMAPII) [39]. In particular, EMAPII acts as proapoptotic factor following different types of stress including hypoxia and mechanical stress. It is worth noting that after its interaction with CXCR4, gp120 promotes p38 MAPK signaling pathway activation and a rapid surface expression and release of EMAPII, thus favoring apoptosis through a paracrine mechanism. In the context of an inflammatory microenvironment, gp120 may also contribute to reduce the EC-derived NO synthesized by the NO synthase that is a major mediator of endothelium-dependent vasorelaxation and endothelial dysfunction.

P17 is a potent angiogenic and lymphangiogenic molecule both *in vitro* and *in vivo*. Activity of p17 is dependent on its interaction with the chemokine receptors CXCR1 and CXCR2, expressed on ECs [40–42]. Angiogenesis and lymphangiogenesis promoted by p17 after its interaction with CXCR1 and/or CXCR2 involve activation of both MAPK/ERK and PI3K/Akt signaling pathways [40–42]. Lymphangiogenesis induced by p17 was found to be partly mediated by the selective release of the pro-angiogenic/lymphangiogenic factor ET-1 [42], which binds to its B receptor (ETBR) expressed on lymph node-derived ECs (LECs) and activates the downstream PI3K/Akt and MAPK/ERK signaling pathways.

Interestingly, many studies demonstrated a long-term persistence of these two structural HIV-1 proteins in lymph node germinal centers and lymphoid tissue of HIV⁺ patients, even during successful cART and in the absence of any detectable viral replication [43, 44].

Interestingly, p17 is continuously released in the extracellular space even in the absence of viral replication and viral protease activity [45] and is detected at nanomolar concentrations in the blood of HIV⁺ patients even in the presence of anti-p17 antibodies [46].

Altogether, these findings suggest that gp120 and p17 are released by infected cells even during cART, bind to ECs, and drive cell activation, angiogenesis, and/or apoptosis, leading to vascular disease. In addition, the capability of p17 to stimulate the immune system and promote a pro-inflammatory status highlights the key role played by this protein in driving endothelial dysfunction.

2.6. HIV-1 regulatory proteins

HIV-1 Tat protein is a trans-activating regulatory protein, which is essential for efficient transcription of the viral genome. Tat is a proto-cytokine promoting several disease conditions by modulating the function of immune cells, mesenchymal cells, and ECs [47, 48].

The HIV-1 viral protein Nef is a 27-kD myristoylated protein. It is not secreted by infected cells, but its interaction with membrane and host cell proteins is crucial to sustain its biological activity. Nef protein is involved in different intracellular functions including alteration of protein trafficking, cell signaling cascades, and inhibition of antibody maturation in B cells [49]. Nef is able to enhance HIV-1 infectivity by promoting the formation of nanotubes connecting HIV-1-infected cells to bystander cells [50]. In particular, transfer of Nef from a HIV-1-infected target cell to ECs through nanotubes supports EC activation, dysfunction, and death [51].

Similarly to many potent angiogenic growth factors such as vascular endothelial growth factor (VEGF) A, Tat has a basic domain rich in arginine and lysine residues that endows the viral protein of a potent and direct angiogenic activity [52, 53]. On the contrary, Nef contains multiple domains capable of interacting with the endocytic cellular machinery [54]. Tat and Nef are both capable of inducing apoptosis in ECs. Many studies demonstrate that Nef is able to induce and activate NADPH oxidase that drives ECs to go for apoptosis. Indeed, by significantly decreasing NO production and increasing superoxide anion production, Nef contributes to reactive oxygen species (ROS) production, cell oxidative stress, and cell death [55, 56]. Moreover, Nef was also found to potently induce EC apoptosis by activation of caspases [57]. Tat causes apoptotic death of ECs via either TNF- α secretion or through activation of the Fas-dependent pathway. Additionally, Tat is able to promote apoptosis in ECs by activating the MAPK/ERK signaling pathway and caspase-3 [58].

In contrast to its proapoptotic effect, Tat may also exert an angiogenic activity through a multi-signaling-dependent pathway. Angiogenic activity promoted by Tat depends on binding and activation of the Flk-1/kinase insert domain receptor (Flk-1/KDR), a VEGF-A tyrosine kinase receptor, and on binding to integrin $\alpha\beta 5$ receptor and heparan sulfate proteoglycans. Tat interaction with cellular receptors leads to the activation of signaling pathways associated with EC growth, migration, and angiogenesis [59, 60].

Similarly to the HIV-1 structural protein p17, both Tat and Nef proteins trigger immune cells activation and inflammation. In fact, Tat promotes transmigration of monocytes through the endothelial barrier and inflammation by inducing ECs to express adhesion molecules as E-selectin, ICAM-1, VCAM-1, and ELAM-1 and to release IL-6 [61, 62]. Tat-induced EC activation is likely aimed to facilitate interaction of inflammatory cells with ECs and promote MCP-1 secretion by activation of PKC signaling pathway [63]. At the same time, Nef protein contributes to inflammation increasing the endothelial MCP-1 production through activation of the NF- κ B signaling pathway [50]. It is worth noting that this activity is also promoted by the HIV-1 structural protein p17, following activation of the AP-1 signaling pathway [32] highlighting a remarkable redundancy in the biological activity of structural and regulatory proteins. Interestingly, it has been recently shown that Nef is also involved in the alteration of

EC cholesterol homeostasis by phosphorylation of Caveolin-1 (Cav-1) at Tyr14 that promotes Cav-1 redistribution and impairment of HDL-mediated cholesterol efflux in ECs [64].

Secretion of Tat in the microenvironment, even during antiretroviral therapy [65]; its direct involvement in endothelial homeostasis, acting as proapoptotic factors or as a pro-angiogenic factor; and its ability to generate an inflammatory status suggest that in the absence of HIV-1 detectable viremia, persistence of endothelial dysfunction in HIV⁺ patients may be, at least in part, ascribed to this (and *bona fide* to Nef) HIV-1 regulatory protein.

2.7. Animal models in HIV-1 endothelial dysfunction

Although many improvements have been made in the development of animal models to study HIV-1-associated endothelial dysfunction, these models do not completely reproduce the pathophysiological features of endothelial dysfunction in humans.

A model of transgenic mice partially reproduces, but below expectations, the features of endothelial dysfunction observed during HIV-1 infection in humans [66]. Indeed, HIV-1-infected mice develop an adventitial mixed inflammatory cell migration, medial hypocellularity, and intimal hyperplasia following smooth muscle infiltration with sparing of the ECs. Furthermore, viral components are observed in smooth muscle cells, which in some instances proliferate in the absence of inflammation, remarking the conceptual principles of viral invasion [66]. The model of macaque species infected with the simian immunodeficiency virus (SIV) shares many more similarities than the transgenic mouse model, in term of disease, with HIV-1 infection and vascular diseases in humans. In an animal model based on macaques infected with a chimeric viral construct containing the HIV-1 Nef gene in a SIV backbone (SHIV-1-nef), the presence of complex vascular lesions has been demonstrated that are not evident in SIV-infected animals [67]. These findings seem to highlight a possible role of HIV-1 Nef in endothelial dysfunction leading to severe arterial disease. Interestingly, vascular alterations, subendothelial infiltration of immune cells, and significantly reduced levels of NO have been found in a model of Rhesus macaques infected by SIV and SHIV-1 [68].

Vasculogenic activity of p17 has been recently demonstrated using *ex vivo* and *in vivo* model [40–42]. The *ex vivo* rat aortic ring assay showed that p17 was able to promote vasculogenesis as potent as that observed using VEGF-A [40]. Similar results were obtained in the *in vivo* chick chorioallantoic membrane (CAM) assay, which highlighted the capability of p17 to generate allantoic neovessels as compared to control CAMs [40]. Matrigel plug assay has been used to test the lymphangiogenic activity of p17 in mice. Matrigel plugs containing the viral matrix protein were implanted into the dorsal subcutaneous tissue of C57BL/6 mice and after 10 days from the injection; matrigel plugs were immunostained with polyclonal antibody to lymphatic vessel endothelial receptor-1 (LYVE-1) identifying pronounced lymphatic vessel formation in p17-treated mice, compared to controls [42]. Interestingly, matrigel plugs containing a p17 variant derived from an Ugandan clade A1, named S75X and endowed with B cell growth-promoting activity, showed the presence of adipocyte infiltration observed at the histological level, thus suggesting that at least some p17 variants may trigger a possible interplay between angiogenesis, lymphangiogenesis, and adipogenesis [41].

3. Conclusions

As described in the present chapter, endothelial dysfunction occurring in HIV⁺ patients may be considered as a multifactorial pathology in which the HIV-1 virus itself and, most of all, its structural and regulatory proteins are able to induce strong changes in the physiology and morphology of ECs by altering their homeostasis and function.

Interestingly, HIV⁺ patients have a high risk of endothelial dysfunction in the absence and in the presence of suppressive cART [69, 70], although low-level transcription of HIV-1 genes continues even after years of cART [71, 72]. Many studies demonstrated the persistence of HIV-1-encoded proteins in different tissues and organs also during pharmacological control of infection. Since these proteins are able to induce a direct endothelial damage and to develop an inflammatory microenvironment, it is possible to hypothesize that viral proteins are among the most important factors involved in endothelial dysfunction development. Although animal models have limitations and can never completely mimic HIV-1 infection of humans or the physiological relevance of a single protein product in the human microenvironment, they start to provide proof of concept for a general vascular dysregulation operated by HIV-1 and its products. Altogether, these data show that a microenvironment disposed to endothelial dysfunction is a common feature in HIV⁺ individuals (**Figure 3**). Recognizing the interaction of some HIV-1 protein products with their receptors as the key events in sustaining endothelial aberrant functioning could help us to identify new therapeutic strategies in combating and/or preventing HIV-1-related vascular disease.

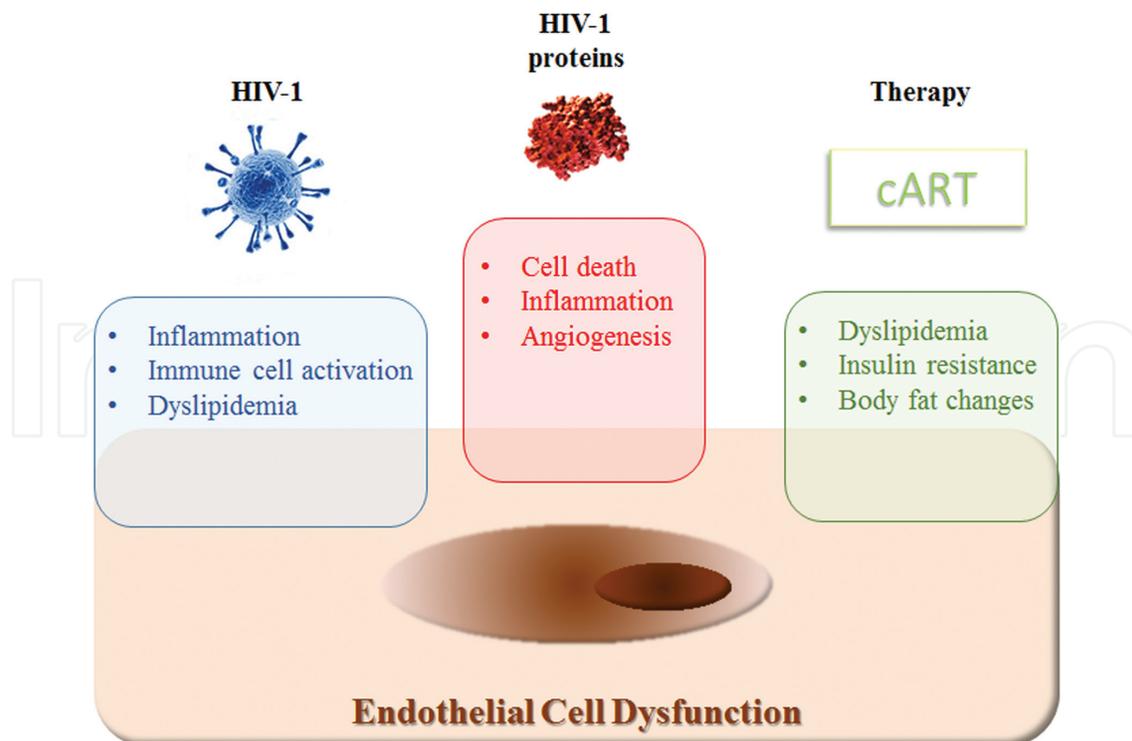


Figure 3. Endothelial dysfunction in HIV⁺ patients under combination antiretroviral therapy (cART) occurs following multiple trigger factors.

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