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The Role of Platelet-Activating Factor in Chronic Inflammation, Immune Activation, and Comorbidities Associated with HIV Infection

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Abstract

With the advent of highly effective antiretroviral therapy, cardiovascular disease has become an important cause of morbidity and mortality among people with treated HIV-1, but the pathogenesis is unclear. Platelet-activating factor is a potent lipid mediator of inflammation that has immunomodulatory effects and a pivotal role in the pathogenesis of inflammatory disorders and cardiovascular disease. Limited scientific evidence suggests that the platelet-activating factor pathway may be a mechanistic link between HIV-1 infection, systemic inflammation, and immune activation that contribute to pathogenesis of chronic HIV-related comorbidities, including cardiovascular disease and HIV-associated neurocognitive disorders. In this review, we examine the mechanisms by which the cross-talk between HIV-1, immune dysregulation, inflammation, and perturbations in the platelet-activating factor pathway may directly affect HIV-1 immunopathogenesis. Understanding the role of platelet-activating factor in HIV-1 infection may pave the way for further studies to explore therapeutic interventions, such as diet, that can modify platelet-activating factor activity and use of platelet-activating factor inhibitors that might improve the prognosis of HIV-1 infected patients.

Keywords

Platelet activating factor; PAF; Lipids; HIV; Inflammation; Immunity; Cardiovascular disease

Introduction

With improved survival, cardiovascular disease (CVD) has become an important cause of morbidity and mortality among people with treated HIV-1 infection[1]. However, the relative

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contributions of viremia, immune activation, antiretroviral therapy (ART), and inflammation to the increased CVD risk are unclear[1]. Inflammation is a well-established contributor to CVD and immune activation is a hallmark of HIV-1 pathogenesis; thus the chronic inflammation associated with HIV-1 infection likely contributes to accelerated atherosclerosis[2]. Inflammation increases production of proinflammatory lipids that mediate atherogenesis[2] and also likely regulate both innate[3] and adaptive immunity[4]. Lipids on both the virus and the host-cell membranes can influence the efficiency of HIV-1 and $CD4^+$ T-cell interactions[5], and oxidized lipids may directly affect HIV infectivity[5].

Platelet-activating factor (PAF) is a mediator of inflammation that is implicated in CVD[6] and HIV-1 infection[7], shares mechanisms of immune activation with oxidized lipoproteins[4], and its receptor (PAFR) is also found on T-cells and macrophages[8]. The main catabolic enzyme of PAF is lipoprotein-associated phospholipase A_2 (Lp-PLA_2) that is found in lipoproteins, is produced by immune cells, can be regulated by oxidized lipids[9], and can affect lymphocyte proliferation and HIV-1 infectivity[10,11]. However, the role of the PAF pathway on regulation of HIV-1 infectivity, systemic inflammation, immunity, and CVD remains to be determined. Further understanding of the interplay between HIV-1 infection, the PAF pathway, and immunity is needed. Herein, we review the available evidence regarding the role of the PAF pathway in HIV-1 immunopathogenesis.

Platelet-activating factor is a potent inflammatory mediator

Platelet-activating factor is a ubiquitous and potent lipid inflammatory mediator[12]. Due to its role, it has been also considered as a hormone or a primitive-universal cellular biological regulator[12]. Platelet-activating factor is identified as 1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine[12]. Even though the majority of ether lipids has been replaced with their esterified analogs during evolution, PAF as some other phosphor glyceryl ether lipids were preserved due to their important biological roles[12]. The term PAF includes a large family of structurally related phospholipids called PAF-like lipids and also several molecules with similar, yet less, PAF action called PAF-like activity molecules[13,14].

Platelet-activating factor is synthesized in many different kinds of organisms such as mammals, plants, and unicellular eukaryotic and prokaryotic cells[15]. In humans it is mainly synthesized in inflammatory-implicated cells such as granulocytes, monocytes, macrophages, platelets, and endothelial cells and also in the cells of many organs (e.g. kidney)[16]. Platelet-activating factor exerts its autocrine and paracrine actions through binding to a well characterized G-protein coupled receptor (PAFR) located on the plasma membrane and nuclear membrane of a wide variety of mammalian cells. Platelet-activating factor binds to its receptor (PAFR), mobilizes $Ca2^+$ and activates numerous signaling pathways such as phospholipase C-mediated signaling[17]. Under physiological conditions, PAF levels are tightly regulated[17]. However, PAF levels can increase by dysregulation of its metabolism (summarized in Table 1) during extended periods of immune activation[17]. Indeed, PAF has a major role in the pathogenesis of numerous inflammatory processes including atherogenesis, asthma allergic, inflammatory skin, and autoimmune disorders such as multiple sclerosis[8].

Platelet-activating factor plays a critical role in cardiovascular disease

Platelet-activating factor and oxidized low-density lipoprotein (OxLDL) rich in PAF-like lipids are directly implicated in atherogenesis[18]. Higher PAF levels are found in animals with severe atherosclerosis compared to healthy controls[19]. There are limited studies about PAF levels in humans and CVD, which reveal that elevated PAF levels were found in patients with coronary heart disease, heart failure, acute myocardial infarction, ischemia, periodontitis, and/or coronary heart disease[6]. The study of PAF and oxidized phospholipids catabolic enzyme, namely Lp-PLA_2, also known as plasma platelet-activating factor acetylhydrolase) remains of great interest because of the contradictory aspects of being, or not, an independent marker of CVD risk due to its dual role in inflammation and oxidative stress[20] and the fact that is associated with both high density lipoprotein (HDL) (HDL-Lp-PLA_2) and LDL (LDL-Lp-PLA_2)[11]. Overall, based on evidence in patients not infected with HIV-1, it is established that PAF is a major inflammatory mediator in the pathogenesis of CVD (Fig. 1).

Platelet-activating factor and platelet-activating factor-like lipids can regulate both innate and adaptive immunity in patients not infected with HIV-1

Platelet-activating factor acts by binding to its receptor (PAFR) found on most cells, including platelets, monocytes, mast cells, granulocytes, B-lymphocytes and dendritic cells[21]. The PAF-like lipids are oxidized phospholipids (OxPL) that also interact with receptors of innate immunity such as toll-like receptors (TLR; e.g. TLR4 and TLR2 which are CD14 dependent) and scavenger receptors (such as CD36) and have pleotropic effects on both innate[22-25] and adaptive[26-30] immunity that can be both anti-inflammatory (Fig. 2) or pro-inflammatory (Fig. 3) depending on the biologic context[22-25,31]. The role of the PAF receptor in the overall biological activity of OxPLs is not well characterized since many effects of OxPLs on target cells are not inhibited by PAF receptor antagonists and not mimicked by PAF[22-25,31]. In addition, OxPLs bind to other receptors, expressed on endothelial cells (ECs), monocytes/macrophages, dendritic cells (DC), and T-cells such as prostaglandin receptors, or they may act through non-receptor mechanisms[32]. Thus, accumulating evidence from HIV-1-uninfected patients indicates that a dynamic cross-talk exists between PAF and immunity since PAF may contribute to and also be affected by changes in immunity (Table 2, Fig. 2 and 3).

Platelet-activating factor may promote chronic inflammation and cardiovascular disease in infections

Platelet-activating factor may induce inflammatory responses in chronic infections. Interactions of the host cells with bacterial lipopolysaccharides lead to increases in PAF biosynthesis as a host response that may act either beneficially or harmfully to the host by reducing infection or promoting chronic inflammation, respectively[33]. For example the bacteria *Helicobacter pylori*[34] and the protozoa *Trypanosoma cruzi*[35] are cases of chronic infections where PAF levels have risen or Lp-PLA_2 is decreased and comorbidities,

including increased vascular permeability and cardiomyopathies, appear. Thus, the PAF pathway may contribute to chronic inflammation in chronic infections that is highly related to myocardial and other organ dysfunction[6].

The cross-talk between platelet-activating factor, HIV-1, inflammation, immunity and chronic comorbidities

Despite the successful advent of ART, persistent immune activation and inflammation are lying behind HIV-infection and are responsible for a plethora of inflammatory manifestations, called "non-AIDS morbidities", such as cardiovascular disease[1]. Residual HIV replication, comorbidities, acute infections, bacterial translocation, as well as complications of ART are some of the main reasons to increase numerous mediators of inflammation and increase all-cause mortality and non-AIDS morbidities[36]. In addition to its immunomodulatory effects as outlined above, PAF may directly affect HIV-1 replication, its metabolism is affected by ART, and limited evidence suggests that the PAF pathway may be implicated as an inflammatory mediator in the pathogenesis of non-AIDS morbidities[7,37-39].

Effects of platelet-activating factor on HIV-1 infectivity

Platelet-activating factor may induce HIV-1 replication through multiple mechanisms. At the early stages of PAF/HIV studies, PAF was considered to be a potential cellular mediator evoking the expression of the HIV genome[40]. The PAF may regulate T-cell proliferation[10] and expression of cell-surface glycoproteins that determine HIV-1 replication[26,27]. The lymphocyte proliferative response is accompanied by membrane lipid metabolism[41]. An essential step for the activation of lymphocytes is the action of PLA_2 in order to release lipids such as arachidonic acid to form the needed phospholipids[42]. Studies reveal that among all types of the PLA_2, independent PLA_2 plays a key role in mediating phospholipid metabolism in order to sustain proliferation[43]. The soluble HIV glycoproteins interact with CD4 to activate PLA_2 in lymphocytes that mediates fusion of virions to the plasma membrane[44]. Finally, PAF may directly affect tumor necrosis factor (TNF)-α signaling that regulates HIV-1 replication[45]. Thus, PAF may regulate HIV-1 infectivity through direct effects on T-cell activation and proliferation, TNF signaling, the expression of cell surface glycoproteins, and the HIV-1 genome.

Effects of HIV-1 on the platelet-activating factor pathway

HIV-1 *per se* may also directly affect the PAF pathway. The viral Tat protein induces PAF biosynthesis[46] through its binding to the receptor of vascular endothelial growth factor-1 (VEGFR-1)[47]. The viral Nef protein induced a 14-fold relative decrease in gene expression of PAFR in human monocyte-derived macrophages of healthy donors[48]. Lipoprotein-associated PLA_2 is increased in both HIV-1-treated and untreated viremic patients compared with control subjects[49] and interferon-α may be implicated in the interplay between HIV-1 and PAF[49]. Thus, there is a dynamic cross-talk between HIV-1 and PAF since HIV-1 affects the PAF pathway and *vice versa.*

Effect of antiretroviral therapy on the platelet-activating factor pathway

In vitro studies suggest that many antiretrovirals, especially protease inhibitors, have potent activity against PAF-induced platelet aggregation (Table 3)[50]. Altered PAF levels and metabolic enzymes are observed in HIV-1-infected subjects on ART compared to HIV-naive volunteers[38]. The combination of tenofovir-DF/emtricitabine/efavirenz is the only ART that is associated with low PAF levels and metabolism, promoting a beneficial anti-inflammatory action in HIV patients (Table 3). On the other hand, abacavir/lamivudine/efavirenz causes a transient increase in PAF levels and enzymes, and it is unknown if this may contribute to the increased CDV risk associated with this ART. Other studies have also shown that the initiation of ART with either a protease inhibitor or nucleoside reverse transcriptase inhibitor did not significantly decrease Lp-PLA_2 activity[49], while the switching from ritonavir-boosted protease inhibitor to raltegravir has decreased Lp-PLA_2 activity[51]. Variability in ART regimens and in characteristics of HIV-1-infected patients may explain differences in the studies regarding the effects of ART on the PAF pathway. Overall, the available data regarding the effects of ART on the PAF pathway are limited in retrospective and *in vitro* studies, and future prospective studies with HIV-1-infected ART-naive patients starting ART are needed to address this question.

A vicious cycle between increased inflammation and platelet-activating factor activity exists in chronic HIV-1 infection

In chronic HIV-1 infection there are increased levels of PAF that induce chemotaxis, cell recruitment and migratory activity of monocytes, vascular permeability, as well as the overall angiogenesis[47,52]. The HIV-infected monocytes overexpress PAF and arachidonic acid metabolites[53]. This HIV-1 replication promotes systemic inflammation and PAF activity (and *vice versa)*[52]. The HIV infection causes acute inflammation, which is characterized by increased PAF levels as a physiological response. The toll-like receptors (TLR) may also mediate the interplay between systemic inflammation and the PAF pathway since PAF activates TLRs and *vice versa*[54]. More specifically, TLRs such as TLR7 and TLR8 are responsible to recognize single-stranded RNA and double-stranded DNA and TLR4 binds to lipopolysaccharides, a product of microbial translocation that mediates immune activation, a hallmark of chronic HIV-1 infection[55,56]. In addition, in chronic HIV-1 infection, the Lp-PLA_2 activity is elevated similarly to other states of infection, inflammation, and CVD[49]. Consistent with the dual anti-inflammatory and pro-inflammatory effects of PAF during acute and chronic infection, respectively (Fig. 2, 3), it is possible that an acute increase in Lp-PLA_2 may be beneficial to the host during acute inflammation, but chronic activation of Lp-PLA_2 activity would result in increased lysophosphatidylcholine formation and favor atherogenesis[10,49]. Thus, the persistent excess of PAF signaling may lead to disorders associated with chronic inflammation and may precipitate a vicious cycle of systemic inflammation and further activation of the PAF pathway.

Increased levels of platelet-activating factor in chronic HIV-1 infection may contribute to chronic comorbidities such as HIV-associated neurocognitive disorders and cardiovascular disease

HIV-1 infection is characterized by a chronic state of immune activation that is an independent predictor of disease and probably the central process causing immune damage and immunosuppression[1]. Although viremia is suppressed with ART, this immune activation does not normalize with therapy and may contribute to chronic complications of HIV-1 infection including CVD[1]. Since PAF may precipitate the vicious cycle of systemic inflammation and immune activation, it may also contribute to these chronic comorbidities. Indeed, the key role of PAF in the pathogenesis of CVD and regulation of immunity has been established (Fig. 2, 3, Table 2). The reported atherogenic activities of OxLDL can be attributed to PAF and PAF-like lipids[18]. The PAF is also a key mediator in the pathogenesis of HIV-associated neurocognitive disorders since it can be a neurotoxin that mediates HIV-infected macrophage-astroglia interactions[53,57]. As a result, the increased PAF levels contribute to or are responsible for the chronic inflammation and the several morbidities such as cardiovascular events and HIV-associated neurocognitive disorders[53,57] (Fig. 4). Further research is needed to pave the way for therapeutic interventions that target the PAF pathway.

Therapeutic implications of the platelet-activating factor pathway in chronic comorbidities associated with HIV-1 infection

A healthy diet may have favorable effects on the platelet-activating factor pathway and may improve morbidity in chronic HIV-1 infection

Medical Nutrition Therapy is an important adjunct in the management of patients infected with HIV[58]. Since HIV patients are at increased risk for CVD, it is important to control metabolic abnormalities and risk factors (dyslipidemia, insulin resistance, and glucose intolerance). In general, a healthy diet low in saturated and *trans* fat should be followed in combination with adequate fiber intake, low intake of simple carbohydrates, alcohol avoidance, and omega-3 supplementation[59,60]. The role of the Mediterranean diet in HIV deserves special consideration. Indeed, the Mediterranean diet has been found to exert beneficial effects in cardiovascular risk factors of patients with HIV[61], while several of its compounds exhibit anti-HIV[62] and anti-PAF activity[63]. For example, extracts of olive oil and whole Mediterranean meals have a PAF inhibitory activity[63,64]. Vitamin D inhibits PAF and atherogenesis in animals[65] and improves antibacterial immunity in HIV-1-infected patients[66]. Interestingly, phenolic compounds, serving as PAF inhibitors[67], also have anti-HIV-1 activity[68], which may imply their indirect role in disease progression through PAF. Moreover, several Mediterranean diet components, such as phenolic compounds, may act on PAF metabolic enzymes[69]. Thus, further studies are needed to establish the potential of healthy diet to improve systemic inflammation associated with the PAF pathway and chronic HIV-1 infection.

Platelet-activating factor and cardiac diseases: therapeutic potential for platelet-activating factor inhibitors

There are numerous molecules that can act as PAF inhibitors that are classified in two groups: specific and non-specific. The first group includes molecules that antagonize, either competitively or noncompetitively, PAF binding to its receptor and may have natural or synthetic origin, with Ginkgo biloba being the most representative[63,70]. On the other hand, non-specific PAF inhibitors inhibit certain components of the PAF-induced signal transduction pathways, such as calcium, G-protein, protein kinase C, and tyrosine kinase along with inhibitors of phospholipases, cyclooxygenases, and lipoxygenases[71]. Prior studies have shown that PAFR antagonists may be a useful therapeutic option for certain chronic comorbidities such as HIV-associated neurocognitive disorders[68,72]. The recognition of PAF as an HIV-induced neurotoxin secreted in the infected brain has led investigators to synthesize PAF antagonists with dual anti-PAF and anti-HIV activity for the treatment of HIV manifestations[68,72]. The modest antiretroviral effect may be due to inhibiting PAF action and TNF-α, which have been shown to enhance viral replication of HIV-1[68]. Finally, oxidized lipids may regulate expression of chemokine receptors important for HIV-1 pathogenesis, such as CCR5 (Fig. 3, Table 2), and thus further studies are needed to elucidate the interplay between ART such as CCR5 antagonists, the PAF pathway, and HIV-1.

Conclusions

Platelet-activating factor is a potent endogenously expressed phospholipid mediator of inflammation that plays a pivotal role in inflammatory responses. Although, the role of PAF in inflammation, CVD, and regulation of immunity has previously been studied extensively in HIV-1-uninfected subjects, the interplay between HIV-1, the PAF pathway, immunity, inflammation, and HIV-1-related chronic comorbidities remain unclear. Limited scientific evidence suggests that the PAF pathway is a mechanistic link between HIV-1 infection and immune activation that drives systemic inflammation and chronic comorbidities including CVD and HIV-associated neurocognitive disorders. Elucidating the role of PAF in HIV-1 infection may set the basis for further studies to explore the efficacy of novel therapeutic interventions (such as PAF inhibitors) that might improve the prognosis of HIV-1 infected patients.

Acknowledgments

Declaration of interest

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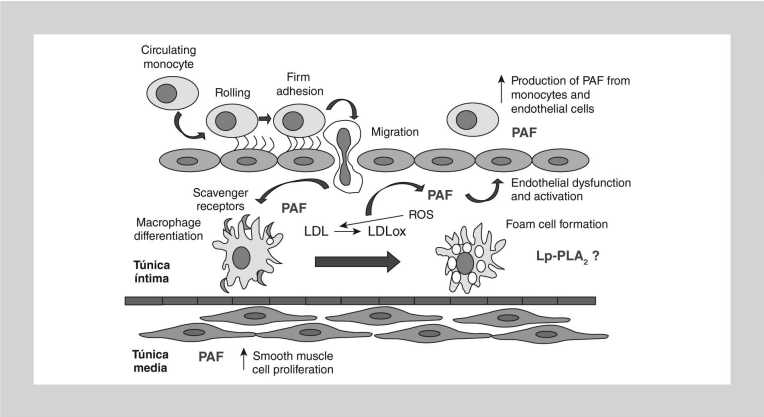

Figure 1.

Platelet-activation factor and its catabolic enzyme have a major role in atherogenesis. The reported atherogenic activities of oxidized low-density lipoprotein can be attributed to platelet-activation factor and platelet-activation factor-like lipids. Platelet-activation factor produced during low-density lipoprotein oxidation leads to endothelial dysfunction and in parallel it induces the release of reactive oxygen species, which leads to further low-density lipoprotein oxidation. Macrophages take up oxidized low-density lipoprotein through scavenger receptors (such as CD36) and form foam cells. The increased platelet-activation factor activity works vice versa as it activates endothelial cells and blood cells to further produce platelet-activation factor and promote atherogenesis. The catabolic enzyme of platelet-activation factor, lipoprotein-associated phospholipase A_2, has dual role in inflammation and oxidative stress and complex effects on atherogenesis. PAF: platelet-activation factor; LDL: low-density lipoprotein; OxLDL: oxidized low-density lipoprotein; ROS: reactive oxygen species; Lp-PLA_2: lipoprotein-associated phospholipase A_2.

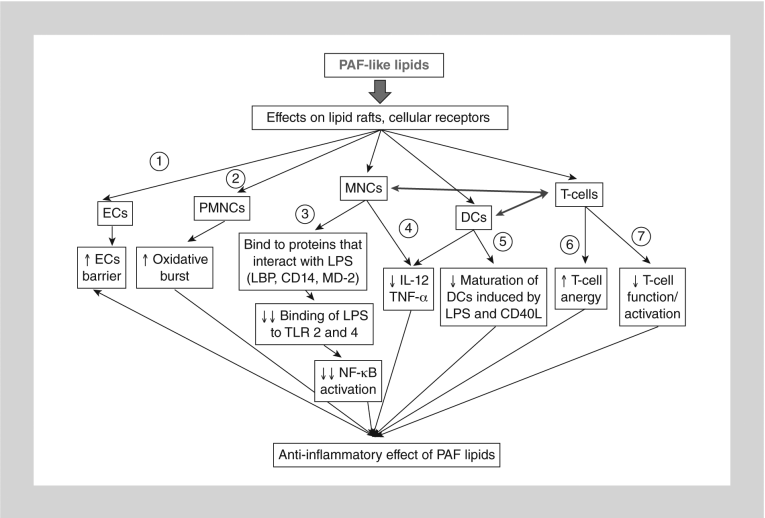

Figure 2.

Anti-inflammatory effects of platelet-activation factor-like lipids included oxidized phospholipids. In the setting of acute inflammation where lipopolysaccharides and lipoteichoic acid expressed on pathogens have major pro-inflammatory effects, anti-inflammatory effects of platelet-activation factor-like lipids on innate immunity are more prominent. The oxidized phospholipids and platelet-activation factor-like lipids (either present in pathogens or in host cells) may have complex effects on endothelial barrier **(1)**. Oxidized phospholipids also inhibit oxidative burst in neutrophil granulocytes **(2)** and action of bacterial endotoxin and nuclear factor-kB activation in monocytes/macrophages via a multi-hit mechanism **(3)**. Oxidized phospholipids were also shown to disrupt lipid rafts, thus preventing formation of signaling complex of toll-like receptor 4 with intracellular adaptors within caveolin-rich membrane domains. In addition, oxidized phospholipids can reduce adaptive immune responses through several mechanisms: a) inhibition of production of proinflammatory cytokines such as interleukin-12 and tumor necrosis factor-α by antigen presenting cells (monocytes/macrophages, dendritic cells) **(4)**; b) inhibition of maturation of dendritic cells induced by lipopolysaccharides and CD40L **(5)**; c) induction of anergy in T-cells and reduced proliferation **(6)**; d) inhibition of T-cell activation and function such as production of pro-inflammatory cytokines (interferon-γ and interleukin-2), cytotoxicity of $CD8^+$ T-cells, and the expression of de novo *synthesized activation markers (CD25)* **(7)**. PAF: platelet-activation factor; EC: endothelial cell; MNC: mononuclear neutrophil cell; LPS: lipopolysaccharide; LBP: lipopolysaccharide binding protein; IL: interleukin; TNF: tumor necrosis factor; DC: dendritic cell; TLR: toll-like receptor; NF-κ*B: nuclear factor kappa B.*

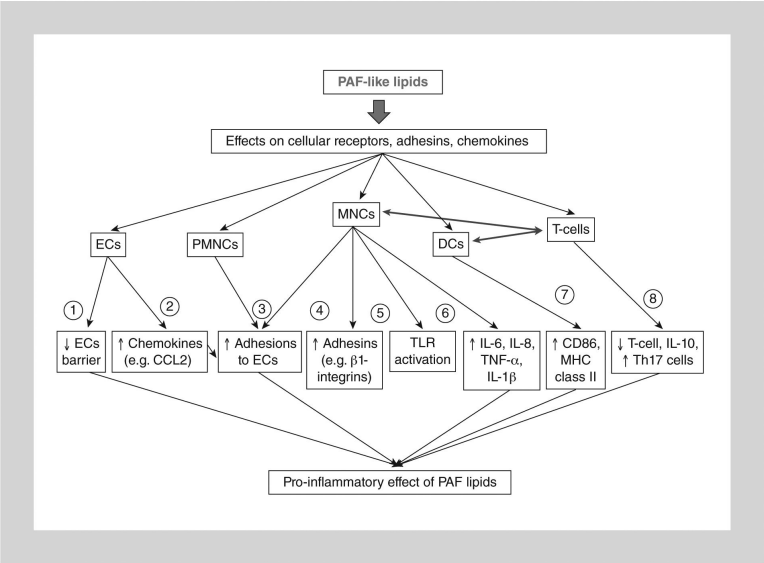

Figure 3.

Pro-inflammatory effects of platelet-activation factor-like lipids included oxidized phospholipids. In the setting of chronic inflammation, pro-inflammatory effects of oxidized phospholipids and platelet-activation factor-like lipids are more prominent. Oxidized phospholipids and platelet-activation factor-like lipids can **(1)** cause endothelial cell barrier dysfunction through multiple mechanisms including reduced expression gap junctions and tight junctions, **(2)** stimulate production of chemokines, **(3)** directly promote adhesion of polymorphonuclear neutrophils and monocytes to endothelial cells, **(4)** upregulate cell adhesions molecules (such as β1-integrins, lymphocyte function-associated antigen-1, P-selectin). **(5)** Under specific conditions or in certain cell types, oxidized phospholipids may be agonistic for toll-like receptor 4 (e.g. through binding to unknown alternative co-receptors other than CD14, **(6)** increase production of pro-inflammatory cytokines such as interleukins-1β, *-6, and -8 and tumor necrosis factor*-α in tissue monocyte-derived macrophages, **(7)** induce surface expression of CD86 and major histocompatibility complex class II in immature dendritic cells, **(8)** reduce production of anti-inflammatory cytokines such as IL-10 from T-cells, interfere with the process of T-cell activation and upregulate formation of Th17, which have been implicated in a number of inflammatory and autoimmune diseases. PAF: platelet-activation factor; EC: endothelial cell; PMNC: polymorphonuclear neutrophil cell; MNC: mononuclear neutrophil cell; IL: interleukin; TNF: tumor necrosis factor; DC: dendritic cell; TLR: toll-like receptor; NF-κB: nuclear factor kappa B; MHC: major histocompatibility complex.

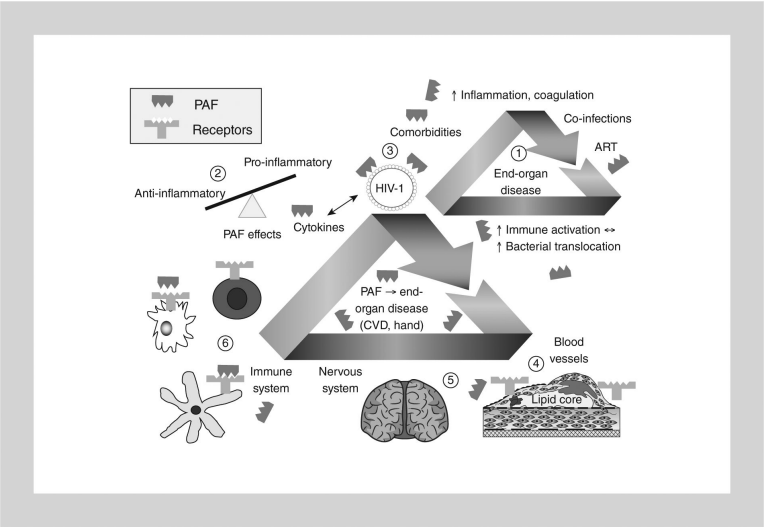

Figure 4.

The crosstalk between platelet-activating factor, HIV-1, inflammation, immunity, and chronic comorbidities. Overall, in chronic HIV-1 infection there is a vicious cycle of increased systemic inflammation, coagulation, immune activation, increased production of oxidized lipids and platelet-activating factor that may directly affect cells and tissues and lead to end-organ disease **(1)**. Platelet-activating factor may exert both pro-inflammatory and anti-inflammatory effects, depending on the biologic context (Fig. 2, 3). In chronic HIV-1 infection, the pro-inflammatory effects are more prominent since there is chronic activation of the platelet-activating factor pathway that may result in increased lysophosphatidylcholine formation **(2).** It is known to increase coagulation and systemic inflammation, affect the pathogenesis of many comorbidities including atherogenesis (Fig. 1), and cause immunomodulation (Fig. 2, 3; Table 2**) (1)**. In addition, there is a dynamic cross-talk between HIV-1 and platelet-activating factor since HIV-1 affects the platelet-activating factor pathway and vice versa **(3)**. Anti-retroviral therapy may also directly affect the platelet-activating factor pathway. Platelet-activating factor has direct effects on vascular permeability, atherogenesis (Fig. 1, Table 2) as well as the overall angiogenesis **(4)**. Platelet-activating factor is a neurotoxin that also mediates HIV-infected macrophage-astroglia interactions and HIV-associated neurocognitive disorder pathogenesis **(5)**. Platelet-activating factor can also cause immunomodulation and affect immune activation through direct effects on granulocytes, monocytes/macrophages, lymphocytes, and dendritic cells **(6)**. The above interactions are not limited to discrete pathways, but are part of interrelated multiple feedback loops. PAF: platelet-activating factor; ART: antiretroviral therapy; CVD: cardiovascular disease; HAND: HIV-associated neurocognitive disorder.

Table 1

Platelet-activating factor metabolism

PAF pathway	Role	Key enzyme(s)
De novo biosynthesis	- Responsible for the constitutive production of PAF - Activated mainly at chronic inflammatory conditions	- PAF-CPT
Remodeling	- Activated at acute inflammatory conditions	- Cytoplasmic PLA_2: converts the ether analogs of PC to Lyso-PAF - Lyso-PAF ATs: acetylate Lyso-PAF to PAF
Catabolism	- Cleaves the acetyl group from sn-2 position forming the Lyso-PAF	- PAF-AHs - In human plasma is called Lp-PLA_2 and circulates bound to lipoproteins

AT: Acetyltransferase; Lp-PLA_2: lipoprotein-associated phospholipase A_2; Lyso-PAF: Lyso-platelet-activating factor; PAF: platelet-activating factor; PAF-AH: platelet activating factor acetylhydrolase; PAF-CPT: platelet-activating factor choline phosphotransferase; PC: phosphatidylcholine; PLA_2: phospholipase A_2.

Table 2

Summary of interplay between platelet-activating factor/platelet-activating factor-like lipids, endothelial barrier, and the immune system (evidence based on HIV-1-uninfected subjects)

Endothelial cells[73]	- ↑ Adhesion between leukocytes, platelets and ECs often through ↑ in chemokines (CCL2, 3, 4, 5, 7, 12, CXCL3, 8, 10, 14, VEGF-A) and CAM (such as P-selectin)
	- May ↑ the endothelial barrier (anti-inflammatory effects)
	- Different OxPLs may ↑ EC permeability and the rolling and tight adhesion of neutrophils to ECs (proinflammatory effects)
Neutrophils[31]	- Stimulate tethering, rolling and tight adhesion of neutrophils to ECs
	- Inhibit oxidative burst in neutrophil granulocytes
Monocytes[24,74]	- ↑ MNC adhesion to activated platelets or ECs often through ↑ of CAM (such as β1-integrins, LFA-1, P-selectin) → → chemokine, cytokine, and tissue factor synthesis
	- ↑ Chemotaxis
	- Can both activate TLRs[54,74] but may also inhibit action of LPS and TLR signaling via a multi-hit mechanism targeting several steps in LPS recognition
	- ↑ Production of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, TNF-α in tissue MDM through activation of both the classical NF-κB and MAPK pathways
	- HDL-associated Lp-PLA_2 can restore the migratory process of MDDC and thus result in resolution of nflammatory reactions in atherosclerotic plaques
Dendritic cells[22,30]	- ↓ Production of pro-inflammatory cytokines such as IL-12 and TNF-α
	- ↓ Maturation of DCs induced by LPS and CD40L
	- ↑ Surface expression of CD86 and MHC class II in immature DCs
	- ↑ Formation of Th17 by ↑ IL-6 and IL-23 production from Langerhans cells
T-cells[23,26-28,30]	- ↑ T-cell anergy
	- High concentrations of PAF ↓ T-cell proliferation
	- Low and physiologically relevant PAF concentrations ↑ $CD4^+$ T-cell proliferation
	- ↓ T-cell activation and CD3 expression
	- ↓ Expression of de novo synthesized activation markers (CD25)
	- ↓ Production of anti-inflammatory cytokines such as IL-10 from T-cells
	- Interfere with T-cell activation: activated but not rested T-cells have membrane high-affinity PAF-binding sites
	- ↓ T-cell function such as production of pro-inflammatory cytokines (IFN-γ and IL-2)
	- ↓ Cytotoxicity of $CD8^+$ T-cells
	- ↑ Formation of Th17

CAM: cell adhesion molecule; CCL: chemokine C-C motif) ligand; CD: cluster of differentiation; CD40L: CD40 ligand; CXCL: chemokine (C-X-C motif) liga d; DC: dendritic cell EC: endot lial cell; HDL: high-density lipoprotein; IL: interleukin; IFN-γ: interferon gamma; LFA-1: lymphocyte fuction-associated antigen-1; Lp-PLA_2: lipoprotein-associated phospholipase A_2; LPS li l accharide; MAPK: mitogen-ativated protein kinase; MDDC: monocyte-derived dendritic cell; MDM: monocyte-derived macrophage; MHC: major histocompatibility complex; MNC: monocyte; NF-κB: nuclear factor kappa beta; OxPL: oxidized phospholipids; PAF: platelet-activating factor; Th: T-helper; TLR: toll-like receptor; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.

Table 3

Effects of antiretroviral therapy on the platelet-activating factor pathway

***In vitro* effects* of ART on PAF pathway**	
NRTI	- Inhibitors: ABV, TDF-DF, FTC, ZDV, DDI, r
	- Weak agonists: DDI, r
NNRTI	- Inhibitors: EFV
	- Weak agonists: EFV
PI	- Inhibitors: ATV, SQV, FPV, IDV, r
	- Weak agonists: ATV, FPV, r
	- Agonists: LPV/r
***In vivo* observations regarding associations of ART with changes in the PAF pathway**	
TDF/FTC/EFV	- ↓ PAF levels and metabolism
ABV/3TC/EFV	- ↑ PAF levels and metabolism
TDF/FTC/ATV/r	- ↑ PAF levels and metabolism
ABV/3TC/ATV/r	- ↑ PAF levels and metabolism

ABV: abacavir; ART: antiretroviral therapy; ATV: atazanavir; DDI: didanosine; EFV: efavirenz; FTC: emtricitabine; FPV: fosamprenavir; LMV: lamivudine; r: ritonavir; IDV: indinavir; LPV/r: lopinavir/r; NLV: nelfinavir; NRTI: nucleoside reverse transcriptase inhibitor; NRRTI: non-nucleoside reverse transcriptase inhibitor; PAF: platelet-activating factor; PI: protease inhibitor; TDF-DF: tenofovir-DF; SQV: saquinavir; ZDV: zidovudine.

*Effects against platelet-activating factor-induced aggregation on washed rabbit platelets.