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Review

The macrophage: the intersection between HIV infection and atherosclerosis

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ABSTRACT

HIV-infected individuals are at increased risk of coronary artery disease (CAD) with underlying mechanisms including chronic immune activation and inflammation secondary to HIV-induced microbial translocation and low-grade endotoxemia; direct effects of HIV and viral proteins on macrophage cholesterol metabolism; and dyslipidemia related to HIV infection and specific antiretroviral therapies. Monocytes are the precursors of the lipid-laden foam cells within the atherosclerotic plaque and produce high levels of proinflammatory cytokines such as IL-6. The minor CD14+/CD16+ "proinflammatory" monocyte subpopulation is preferentially susceptible to HIV infection and may play a critical role in the pathogenesis of HIV-related CAD. In this review, the central role of monocytes/macrophages in HIV-related CAD and the importance of inflammation and cholesterol metabolism are discussed. *J. Leukoc. Biol.* 87: 589–598; 2010.

Introduction

Clinical and epidemiological studies have consistently connected HIV infection with increased risk of CAD across large cohorts and databases. People with HIV infection have 1.5- to twofold higher incidence of cardiovascular events reported compared with uninfected individuals [1–4]. Recently, a large retrospective analysis of healthcare data performed by Triant et al. [5] suggested that HIV infection independently confers an odds ratio for acute myocardial infarction of ~2.07 (95% CI, 1.31–2.61) after adjusting for traditional risk factors such as age, hypertension, diabetes, and dyslipidemia. Surrogate markers of CAD, such as carotid artery IMT, indicate that HIV infection is also accompanied by an increase in atherosclerosis [6–8]. Carotid artery thickening was up to 24% higher in HIV-infected patients compared with uninfected sex- and age-matched persons, and was comparable in CART-naïve patients and those with virologic suppression on CART [8], pointing to HIV as an independent risk factor for atherosclerosis.

There are several potential mechanisms by which HIV infection may increase the risk of CAD, including chronic immune activation and inflammation, secondary to HIV-induced microbial translocation and low-grade endotoxemia; the direct effects of HIV and viral proteins on macrophage cholesterol metabolism; and dyslipidemia related to specific antiretroviral therapies (depicted in **Fig. 1**). A difficulty in dissecting the pathogenetic mechanisms underlying HIV-related CAD arises from the strong influence of specific CART regimens together with higher rates of certain traditional risk factors for CAD in some HIV cohorts [9]. Results from the DAD study group demonstrated that the relative risk of myocardial infarction was 1.16/year for the CART cohort [9], similar to that associated with smoking or diabetes. The same traditional risk factors for CAD exist in HIV-infected and uninfected subjects, but male sex, smoking, and dyslipidemia may be disproportionately higher in some HIV cohorts. In contrast, other risk factors, such as obesity, may be under-represented in HIV-infected men. HIV infection per se may be an independent risk factor for CAD [5]. Emerging paradigms for more direct effects of HIV infection on the cardiovascular system include recent evidence that HIV infection is associated with chronic immune activation and systemic inflammation [10], secondary to microbial translocation (discussed below), and the effect of HIV-1 protein Nef on ABCA1, the key mediator of reverse cholesterol transport [11]. HIV-induced immune activation may

Abbreviations: ABCA1=ATP-binding cassette transporter A1, Apo=apolipoprotein, Apo-/-=Apo-deficient, CAD=coronary artery disease, CART=combination antiretroviral therapy, CI=confidence intervals, CRP=C-reactive protein, DAD=Data Collection on Adverse Events of Anti-HIV Drugs, ECM=extracellular matrix, HDL=high-density lipoprotein, hsCRP=highly sensitive CRP, IMT=intima-media thickness, LDL=low-density lipoprotein, PI=protease inhibitor, RCT=reverse cholesterol transport, s=soluble, SMART=Strategies for Management of Antiretroviral Therapy

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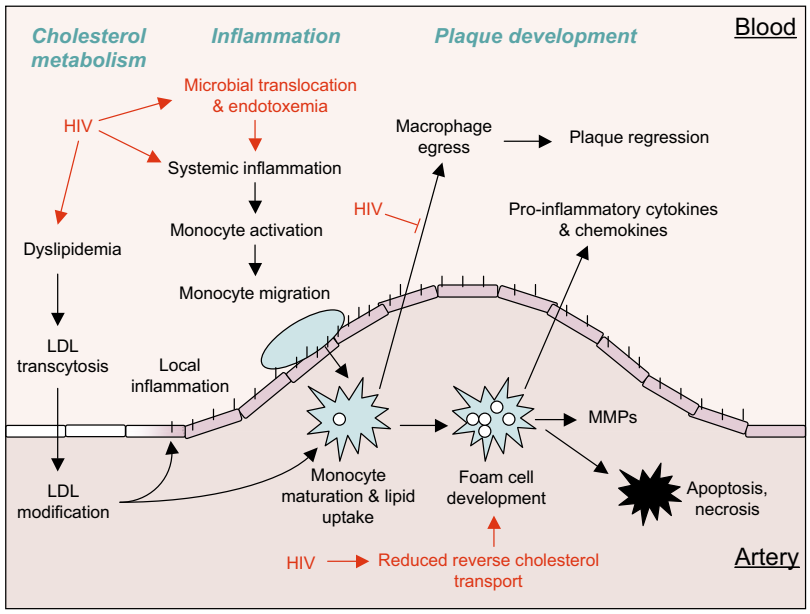

Figure 1. Potential mechanisms of heightened atherogenesis in HIV infection. Two primary risk factors of cardiovascular disease are chronically elevated plasma LDL and/or decreased HDL, and inflammation-driven activation of monocytes and vascular endothelium with heightened migration of monocytes into the atherogenic lesion and maturation into macrophages and lipid-rich foam cells. Plaque regression is associated with emigration of macrophages from the plaque [118], whereas chronic foam cell accumulation, together with their production of proatherogenic factors and their ultimate apoptosis and necrosis in a hypercholesterolemic patient, causes plaque expansion and plaque instability, ultimately resulting in cardiovascular event(s). HIV infection is likely to affect each stage of this process (indicated in red), thereby increasing risk of cardiovascular disease above the effects of traditional risk factors. *Dyslipidemia*: Specific antiretroviral drugs (e.g., PIs) are associated with dyslipidemia (increased plasma LDL and triglycerides, decreased HDL). HIV infection itself may also promote dyslipidemia as a result of changes in cholesterol metabolism. *Systemic inflammation*: Plasma levels of proinflammatory cytokines may be increased in viremic HIV-infected individuals, and HIV-associated microbial translocation across gut epithelium results in chronic endotoxemia [10]. Monocyte activation has been demonstrated in viremic HIV-infected individuals and is ameliorated only partially during virological suppression [42]. Whether viremia-induced IFN-α production and adaptive T cell responses have additional proatherogenic effects is not known. *Macrophage egress*: Reverse transendothelial migration of monocyte-derived macrophages from the plaque requires basal-to-apical migration across the vascular endothelium, which is defective in HIV-infected macrophages in vitro [109]. *Accumulation of foam cells*: Internalization of extracellular lipoprotein and development of lipid-laden foam cells are associated with reduced migratory capacity [120]; defective cholesterol efflux by HIV-infected macrophages is likely to promote foam cell accumulation in plaques [11]. Foam cells also produce proatherogenic factors such as chemokines, cytokines, and matrix metalloproteinases (MMPs), which promote plaque expansion and instability and can undergo apoptosis and/or necrosis in hypercholesterolemic settings.

also be associated with premature immune senescence [12], resulting in an increased risk of diseases related to aging, including CAD.

Monocytes play a critical role in atherogenesis and HIV disease. Monocytes develop initially in the bone marrow, emigrate into peripheral blood, from where they provide routine immunosurveillance or respond to infection/inflammation, and are subsequently delivered to tissues, where they differentiate into macrophages [13]. In humans, peripheral blood monocytes may be divided into at least two major subsets: a minority subset of monocytes expresses CD16 and has variable expression of CD14, produces more inflammatory cytokines, and expresses higher levels of TLR-4 compared with the majority CD14+/CD16– monocyte population [14–16]. Monocytes are precursors of the macrophages within atherosclerotic lesions, including lipid-laden foam cells [17–19], and lesion-associated macrophages represent a major source of a number of cytokines and chemokines that direct monocytes into vascular lesions, thus creating a positive-feedback loop, although the roles of the two monocyte subsets are poorly characterized. Changes that occur in monocytes and macrophages during HIV-1 infection are likely to impact on atherogenic processes. During HIV-1 infection, monocytes display an activated phenotype, although correlates of monocyte phenotype and cardiovascular disease are poorly characterized. Additionally, HIV interferes with the ability of macrophages to handle excessive cholesterol by inhibiting cholesterol efflux [11]; both of these mechanisms may impact on initiation and progression of atherosclerotic plaques.

Monocyte differentiation is tightly associated with the propensity to initiate formation of an atherosclerotic plaque as well as susceptibility to HIV infection: Although monocytes are relatively resistant to HIV infection, differentiated macrophages are highly susceptible [20–22]. In vivo, only a small proportion of peripheral blood monocytes (0.001–1%) is infected with HIV-1 at any given time throughout the course of infection [23, 24], whereas a much higher proportion of tissue macrophages harbors HIV-1 [25, 26]. The CD14+/CD16+ monocyte subset is preferentially infected with HIV, in vivo and in vitro [27, 28]. The reason for relative resistance of the majority of monocytes to HIV-1 infection is hotly debated, and possible mechanisms include lower expression of HIV receptor/coreceptors [20], expression of anti-HIV micro RNAs [29, 30], or expression of antiretroviral restriction factors [27, 31, 32], in particular, ApoB mRNA editing enzyme catalytic polypeptide-like 3G (APOBEC-3G) complexes [27]. CD14+/CD16+ monocytes may play a crucial role in the pathogenesis of HIV-related CAD as an important source of IL-6 and other proinflammatory cytokines.

Atherosclerotic plaques contain a variety of immune cells, including T cells, B cells, and NK cells, and their role in atherosclerosis has been reviewed recently elsewhere [33]. The specialized roles of monocytes and macrophages in atherogenesis and the pathogenetic effects of HIV-1 infection on these cells are the focus of this review. We propose that HIV infection produces a proatherogenic phenotype in cells of macrophage lineage that has an additive effect on CAD prevalence and prognosis over and above traditional CAD risk factors.

HIV-RELATED ATHEROGENESIS: ROLE OF INFLAMMATION

Chronically elevated cholesterol, and in particular, LDL cholesterol, is considered the driving force behind atherosclerosis and CAD (see below). However, chronic inflammation is also an essential element of the pathogenesis of atherosclerosis. The role of inflammation in atherosclerosis has been confirmed by a number of mechanistic studies (for reviews, see refs. [33, 34]), as well as the strong association between clinical manifestations of atherosclerosis and the most sensitive marker of inflammation, CRP [35, 36]. In addition, systemic inflammatory disorders are commonly associated with an increased risk of atherosclerosis [37]. However, clinical data, confirming that treatment of inflammation slows development of atherosclerosis, are still missing. Among the many manifestations of inflammation, the elements relevant for development of atherosclerosis include those responsible for enhanced migration of monocytes across the endothelial lining of the blood vessel, their inhibited emigration from the vessel wall, and modification of lipoproteins inside the vessel wall. Specifically, these include induction of expression of adhesion molecules on endothelium [38] and monocytes [39, 40] and secretion of chemokines attracting leukocytes to the vessel wall [41] (described in detail below).

Systemic inflammation

Systemic inflammatory immune responses are strongly associated with increased risk of CAD (recently reviewed in ref. [33]). Of the proinflammatory cytokines, IL-6 is one of the major inflammatory markers associated with carotid atherosclerosis and stenosis [42], and IL-6 decreases lipoprotein lipase activity (required for metabolism of circulating triglycerides) and increases macrophage uptake of lipids [43]. IL-18 is produced by macrophages during the early stages of the inflammatory response [44] and is elevated in the plasma of individuals with hypertension and increased carotid IMT [45]. Acute-phase proteins such as CRP are induced primarily by IL-6, together with IL-1 and TNF-α, and activate monocyte production of proinflammatory cytokines (e.g., IL-6, M-CSF) in a positive-feedback loop [46], decrease anti-inflammatory IL-10 production [47], increase monocyte CD11b expression and endothelial adhesion [48], and increase endothelial production of the monocyte-recruiting chemokine CCL2 [49]. CRP is a member of the pentraxin family of proteins produced by the liver, which is associated with endothelial dysfunction, and is an accepted marker of coronary vascular disease when measured using a hsCRP assay ([50]; reviewed in refs. [51, 52]). IL-6 and M-CSF favor differentiation of monocytes into activated macrophages during inflammatory responses [53]. Studies of genetic polymorphisms in *CRP*, *IL-6*, and its receptor *IL-6R* loci suggest that although IL-6 may be causally related to CAD, CRP is more likely to be a surrogate marker of CAD [54, 55]. On the other hand, it was demonstrated recently that monomeric CRP has a dramatic effect on monocyte activation and adhesion, suggesting a causative role for CRP in CAD [56]. It is plausible that CAD induction by IL-6 also occurs via monocyte activation.

Plasma levels of a number of proinflammatory cytokines are increased in HIV-infected individuals [57–59] and persist during HIV infection, even in patients with low residual viremia (viral load $\leq$20 copies/ml), in whom plasma contains increased levels of soluble immune activators (e.g., TNFRII) [60], although other recent studies suggest decreased production of proinflammatory cytokines by monocytes from individuals receiving CART [10, 61, 62]. Elevated plasma cytokines also persist during treatment interruption [63], and elevated levels of plasma IL-6 and IL-6 mRNA are generally found in patients with HIV infection [64–66]. In the SMART study, interruption of CART was associated with an increase in mortality, including cardiovascular mortality, postulated to be a result of heightened immune activation and systemic inflammation [67] and strongly associated with raised levels of plasma IL-6 [68]. Elevated IL-6 levels have also been linked with mortality (including cardiovascular mortality) in patients treated with the nucleoside analog abacavir [68]. In a combined analysis of patients enrolled in SMART and DAD study groups, the adjusted hazard ratio for myocardial infarction with current use of abacavir was 4.3 (95% CI 1.4–13.0) [69]. IL-18 is also increased in the plasma of HIV-infected individuals compared with seronegative subjects [70, 71]. Plasma levels of IL-18 correlated with atherosclerotic plaque dimensions in acutely SIV-infected rhesus monkeys fed on an atherogenic diet [72]. Whether plasma levels of IL-18 are increased in HIV-infected individuals with myocardial infarction has not yet been reported.

Levels of CRP, measured using the hsCRP assay, are elevated in patients with HIV infection [73–75], are negatively correlated with CD4 counts [76], and independently predict HIV disease progression and mortality [77]. Levels of CRP are independently associated with risk of myocardial infarction in this population, with an odds ratio for acute myocardial infarction in HIV-infected individuals who have an elevated CRP greater than fourfold when compared with those without HIV infection and with normal CRP levels [5]. D-dimers, byproducts of fibrinogen degradation via thrombin, factor XIII, and plasmin, are also markers of the acute-phase response, and increased levels have been reported in patients with all-cause mortality during CART interruption in the SMART study [68]. In general, CART reduces D-dimer levels [78]. The extent to which chronic immune activation in HIV patients is correlated with elevation of acute-phase reactants and hence, increased CAD risk remains to be determined.

Although the immune response to HIV replication is likely to be a major source of elevated plasma cytokines, HIV infection is also associated with extensive damage to gut mucosa, followed by increased translocation of microbial components from the gut into the bloodstream [10]. Plasma LPS-binding proteins, such as sCD14 and the accessory protein for TLR-4 signaling, MD-2, are markers of microbial translocation that are elevated in HIV infection [10, 79–81] and are associated with HIV disease progression in Western [82], although not in African [83], cohorts. Microbial translocation across the gut mucosa causes low-grade endotoxemia, which has shown a strong association with chronic low-level systemic inflammation and activation of the peripheral T cell compartment [10] and monocytes [79]. Interestingly, a study of CART interruption suggests that plasma LPS levels are not elevated until a relatively long period (>12 weeks) of detectable HIV viremia [84]. In this study, immune activation, at least in the T cell compart-

ment, was not correlated with endotoxemia and was more likely to be driven by HIV-specific immune responses. Given the up-regulation of acute-phase responses and proinflammatory cytokine levels in plasma and activation of monocytes and vascular endothelium in HIV-infected individuals, it is possible that increased microbial translocation during chronic HIV infection is linked pathogenetically to the increased risk of CAD in HIV-infected individuals. Indeed, in a model of chronic low-grade inflammation, treatment of mice with low levels of LPS induced development of coronary artery fibrosis and early atheroma formation [85]. It was reported recently that initiation of CART does not reduce levels of proinflammatory cytokines found in the colonic mucosa, even after 9 months of treatment [86]. The effects of chronically elevated microbial translocation into the bloodstream on the systemic cytokine milieu in the setting of HIV infection remain to be elucidated.

Monocyte activation

Despite the strong evidence for associations between immune activation and CAD, there is relatively limited information about the activation status of monocytes in individuals with a higher risk of CAD. CD14+/CD16+ monocytes normally represent 5–15% of circulating monocytes [87], and this subset is considered "proinflammatory" as a result of greater production of TNF-α in response to inflammatory mediators such as LPS [14]. In a study of renal dialysis patients (in whom the risk of CAD is 40–400 times that of age-matched, healthy individuals), higher levels of the CD14+/CD16+ monocyte subset were associated with increased CAD-related events [88]. In murine models of CAD, such as ApoE−/− mice fed on a high-fat diet, numbers of blood monocytes (identified according to CD115/M-CSFR expression) are elevated, suggesting mobilization of the monocyte compartment during hyperlipidemia [89]. Tacke et al. demonstrated that the murine equivalents of human CD14+/CD16– monocytes, which have high surface expression of CCR2 and myeloid marker Ly6 (CCR2+Ly6^{high}), undergo efficient accumulation in atherosclerotic plaques [89]. In comparison, the murine CCR2-negative Ly6^{low} monocytes, corresponding to human CD14+/CD16+ monocytes, develop a CD11c+ dendritic cell phenotype following migration into plaques, indicating different roles for the monocyte subsets during plaque development. In other studies of ApoE−/− mice, CD11c+ monocyte numbers were increased, and a deficiency in CD11c (CD11c−/− mice) reduced macrophage accumulation in atherosclerotic lesions [40]. Further evidence is provided by experiments where the cardioprotective HDL reduced monocyte activation by inhibiting CD11b activation [39].

Monocytes from HIV-infected patients possess many characteristics of activated monocytes, e.g., spontaneous production of proinflammatory cytokines [62] and expression of activation markers CD38, CD69, and CD11b, antigen-presentation molecules HLA-DR and CD86, and decreased CD62L [61, 79, 90–93] (Gregor Lichtfuss, A. Jaworowski, and S. M. Crowe, unpublished data). Early studies indicated that the proportion of CD14+/CD16+ monocytes was increased in HIV-infected individuals [94, 95] in comparison with the major CD14+ subset. Our laboratory has shown that the CD14+/CD16+ monocyte subset is expanded in HIV-infected subjects who are CART-naïve or have discontinued CART, compared with those receiving CART, in which CD16 expression is similar to that of uninfected control donors [96]. Monocytes from HIV-infected individuals also have higher expression of the activation markers CD69 and HLA-DR, and expression of these markers correlates with plasma LPS levels [79, 92].

Monocyte migration

Under normal circumstances, leukocytes minimally adhere to the endothelium, and there are few macrophages inside the vessel wall. However, local inflammation, caused by hyperlipidemia, shear stress, or endothelial damage, induces apical expression of adhesion molecules such as P-selectin glycoprotein-1 [97] and cellular adhesion molecules VCAM-1 and ICAM-1 [98] on endothelium. Systemic inflammation, on the other hand, induces increased numbers of monocytes and increased expression of leukocyte adhesion molecules, such as CD11b (membrane-activated complex 1) [40, 89, 99]. Together, these adhesion molecules increase leukocyte tethering and rolling along the apical surface of activated endothelium and leukocyte arrest and crawling to interendothelial junctions via CD11b/ICAM-1 interaction [100, 101], which is followed by transendothelial migration into the subendothelial space.

Mouse studies indicate that migration of monocytes into inflammatory arterial lesions is essential for atherogenesis (reviewed in ref. [102]). The situation is complicated by the existence of different monocyte subsets that show different migratory properties. Chemokine receptor expression patterns suggest that the minor human CD14+/CD16+ subset may be functionally equivalent, at least in part, to the Gr1– murine subset and expresses higher levels of CXC_3R1 (fractalkine receptor) and CCR5. The CD14+/CD16– subset is functionally equivalent to the murine Gr1+ subset and expresses high levels of CCR2 [13]. Thus, these monocyte subsets have differing expression of chemokine receptors CCR2, CX_3CR1, and CCR5 that are important for entry into atheromatous lesions [89]. Mouse CCR2−/− [103], CCR5−/−, and CX_3CR1−/− [89, 104] knockout models have shown significantly reduced atherosclerotic lesion development and decreased monocyte infiltration into arterial vessel walls. MCP-1 (CCL2; the ligand for CCR2) also plays an important role in transendothelial migration and atherogenesis, as a critical chemoattractant for CD14+/CD16– monocytes into the subendothelial space, where they can develop into foam cells. Emerging roles of chemokines in monocyte biology include regulation of bone marrow production of monocytes and prosurvival signaling, which may also contribute to atherogenesis. It was demonstrated recently that CX_3CR1 provides an antiapoptotic signal that promotes survival of monocytes and/or foam cells in atherogenesis [105]. Interestingly, CX_3CR1 was not required for entry of murine CX_3CR1^{hi} (CD14+/CD16+ equivalent) monocytes into atherosclerotic lesions [89, 106], which instead, partially depended on CCR5. CCR2 directs the release of monocytes from bone marrow under inflammatory conditions [107], and CCR2 knockout mice showed reduced monocytosis in hypercholesterolemia [108], although this may not be restricted to CCL2 [106]. A large reservoir of undifferentiated monocytes in the spleen, which is mobilized rapidly to the bloodstream

during ischemic myocardial injury, has been characterized recently [109] and raises the question of whether conditions such as hypercholesterolemia and endotoxemia cause similar mobilization of monocytes from sites other than bone marrow. CCR2+ (CD14+/CD16− equivalent) monocytes require CCR2, CX_3CR1, and CCR5 for entry to atheromatous lesions [89]. The routine patrolling of the endothelium by CX_3CR1^{hi} monocytes enables rapid entry of these cells into sites of inflammation [109], although whether this process is involved in initiation of fatty lesions is not known.

Little is known about monocyte transendothelial migration in the setting of HIV infection, although we and others have shown that HIV infection in vitro augments expression of β-2 integrins including CD11a/CD18 and CD11b/CD18, which promote cell adherence to the endothelium [110, 111]. In CART-naïve, HIV-infected individuals, markers of endothelial activation (sICAM-1 and sVCAM-1) are elevated in plasma [112]. Fibronectin fragments, which are the product of proteases induced under inflammatory conditions and are present in circulation of many HIV+ individuals, have been shown to stimulate transendothelial migration of HIV-infected mononuclear cells, where they clustered just under the endothelial monolayer [113]. It is therefore likely that systemic inflammation associated with HIV infection may promote migration of monocytes across the vascular endothelium; however, this is yet to be demonstrated. The converse process of emigration of macrophages out of plaques was recorded in early electron microscopy investigations, which showed that lipid-laden macrophages can be visualized emigrating from plaques across the vascular endothelium [114]. Using an in vitro model of HIV-infected, monocyte-derived macrophages, we have shown that HIV infection reduced reverse transendothelial migration from a collagen matrix across a confluent endothelial monolayer [115]. To the extent that this occurs in macrophages present within an atherosclerotic plaque, this observation supports the hypothesis that HIV may contribute to the increased risk of CAD through persistence of macrophages within a developing plaque, a prerequisite for the formation of foam cells.

CHOLESTEROL METABOLISM AND ATHEROSCLEROTIC PLAQUE DEVELOPMENT

Local inflammation with accumulation of macrophages in the arterial wall represents an early, inflammatory stage of development of atherosclerosis. Accumulation of cholesterol in plaque-associated macrophages is a hallmark of advancing atherosclerosis and the key driver of atherosclerosis. The earliest manifestation of atherosclerosis, a fatty streak, is characterized by appearance of cholesterol-laden macrophages in the vessel wall; the end-stage of atherosclerosis, a ruptured plaque, is characterized by a necrotic core filled with cholesterol deposits [116]. Parameters of cholesterol metabolism constitute up to 80% of amendable risk of atherosclerosis, and interventions affecting cholesterol homeostasis are by far the most effective way to prevent and in some instances, reverse atherosclerosis.

With the exception of hepatocytes and adrenocortical cells, human cells are unable to metabolize cholesterol, and hence, intracellular cholesterol content is fully dependent on a balance between rates of cholesterol delivery to and removal from cells. There are three pathways of cholesterol delivery: cholesterol biosynthesis, LDL receptor-mediated uptake of native lipoproteins (mostly LDL), and scavenger receptor-mediated uptake of modified lipoproteins. The two former pathways are present in all cell types and are tightly regulated by the sterol receptor element-binding protein regulatory system, effectively preventing oversupply of cholesterol through these pathways [117]. The latter pathway is not tightly regulated, and the amount of cholesterol entering the cell is determined mainly by the extracellular concentration of modified lipoprotein particles [118]. Uptake of modified lipoproteins is particularly active in macrophages, via CD36 and ScR A-I/II [119], although high levels of pinocytosis by foam cells have been demonstrated recently, suggesting receptor-dependent and independent mechanisms of uptake [120]. This reflects one of their biological roles—that of removing modified proteins and protein complexes from tissues [121].

When macrophages are exposed to a high concentration of modified lipoproteins, the increased flow of cholesterol into cells through scavenger receptors can no longer be compensated by reducing LDL receptor-mediated lipoprotein uptake and cholesterol biosynthesis, and intracellular cholesterol is raised to a dangerous level. Macrophage cholesterol content must be maintained within very narrow limits, as falling behind or exceeding these limits triggers necrosis or apoptosis [122]. Although deficiency of cholesterol can normally be overcome by enhanced cholesterol biosynthesis and/or LDL uptake, excessive cholesterol presents a greater problem. Cells use two active mechanisms to remove excessive cholesterol. One is cholesterol efflux, removing cholesterol to an extracellular acceptor, most often HDL [123]. If the capacity of the cellular pathways of cholesterol efflux is inadequate, or there is an insufficient quantity of the extracellular acceptor available, another pathway is engaged—that of esterification of excessive cholesterol and incorporation of neutral cholesteryl esters into lipid droplets. Although the latter may relieve cells of excessive cholesterol in the short term, when imbalance between cholesterol delivery and removal persists, lipid droplets gradually fill most of the cytoplasm affecting a normal cellular metabolism, and the macrophage becomes a foam cell.

Foam cells, in addition to their large size and reduced mobility, express various adhesion molecules on their surface; as a result, their capacity to emigrate from the plaque is reduced significantly [124, 125]. Additionally, modified lipoprotein uptake by CD36 can impair cytoskeletal remodeling required for cell migration [126]. Foam cells also secrete cytokines attracting monocytes to the plaque. Together, increased migration of monocytes to the plaque and reduced emigration of macrophages from the plaque lead to the accumulation of macrophages in the plaque; thus, increased cholesterol content leads to imbalance of the cellular content in the vessel wall [124] and exaggerates the inflammation. Further, as foam cells are no longer capable of compensating for excessive intracellular cholesterol content by synthesizing cholesteryl esters, the concentration of unesterified cholesterol rises beyond the threshold, triggering cellular apoptosis and necrosis [127]. Dead

macrophages release proteases causing degradation of ECM and necrosis of surrounding cells, including endothelial cells that cover the plaque; they also leave behind a large quantity of cholesterol, which can be taken up by other macrophages (and thus, exaggerate the problem even further) [127] or form insoluble cholesterol crystals [128]. A plaque with a necrotic core filled with cellular remains and cholesterol is unstable and has high propensity for rupturing, causing an acute vascular event. A recent study suggests that plaque rupture and associated hemorrhage promote development of a minor population of macrophages that express CD163, a receptor for haptoglobin-hemoglobin complexes [129]. CD163+ macrophages display an anti-inflammatory phenotype, and the authors speculate that the primary purpose of these cells is hemoglobin uptake and plaque stabilization. The role of macrophages within plaques is therefore not limited to cholesterol metabolism, and diversity of macrophages within plaques requires further exploration (recently reviewed in ref. [130]).

Although an imbalance of cholesterol metabolism is central to the pathogenesis of advanced atherosclerosis, this is insufficient for atherosclerosis to develop, and mechanisms of atherosclerosis are not limited to the impairment of the lipid metabolism. For the events described above to occur, leukocytes need to continue to migrate into the subendothelial space of the vessel wall, and monocytes should differentiate into macrophages and not emigrate before they become foam cells. Lipoproteins need to penetrate the endothelium, and their modification needs to be recognized by scavenger receptors. The development of atherosclerotic plaque requires smooth muscle cells to migrate to the vessel intima, change their phenotype, and synthesize increased quantities of ECM proteins [116]. Chronic elevation of plasma LDL, sequestration of LDL in the subendothelial compartment, and subsequent LDL modification not only present an ample source of cholesterol but also promote early vascular lesions as a result of the highly inflammatory effects of oxidized LDL on endothelium (reviewed in refs. [33, 131]). Endothelial activation and inflammation trigger leukocyte migration across the vascular endothelium into the inflamed vessel wall (as described above). All elements of pathogenesis of atherosclerosis may potentially be modulated by HIV infection.

Furthermore, inflammation and imbalance of lipid metabolism are not separate elements of pathogenesis of atherosclerosis; they are tightly related to each other, and mechanistic relationships between them have begun to emerge only recently. The key elements of this inter-relation are two classes of nuclear receptors—peroxisome proliferator-activated receptors and liver X receptors [132, 133]—and TLRs, such as TLR-2, -3, and -4 [134–136]. Monocytes express the highest levels of the predominant endotoxin receptor, the TLR-4/CD14 complex, of any blood cell type, such that CD14 is used as the principal identifying marker for monocytes in blood. Oxidized LDL, which is increased in atherosclerosis, not only stimulates secretion of proinflammatory cytokines but also up-regulates the expression of TLRs (particularly TLR-4) on macrophages within the newly forming plaque, resulting in cellular activation and inflammation and contributing to atherogenesis [137, 138]. Another crossing point between inflammation and lipid metabolism is the fact that many inflammatory as well as anti-inflammatory proteins are transported in the bloodstream by lipoproteins, e.g., transport of serum amyloid A and complement components by HDL, and accumulation of lipoproteins in the subendothelial space is associated with accumulation of pro- or anti-inflammatory proteins [139, 140]. Thus, local and systemic inflammation is an important risk factor and key pathogenic mechanism underlying development of atherosclerosis.

CHOLESTEROL METABOLISM AND HIV INFECTION

CART-related dyslipidemia

The contribution of CART to risk of CAD is illustrated by the detrimental effects of intermittent therapy, as reported in the SMART study [69, 141, 142], as well as the effects of specific regimens, especially those containing PIs and the nucleoside RT inhibitor abacavir [9, 143]. All PIs are not equal, however, and atazanavir appears to have reduced effects on dyslipidemia compared with other PIs such as indinavir or ritonavir [144]; however, the implications of these differences on cardiovascular risk are yet to be established. The PIs are also causally associated with development of lipodystrophy, hypercholesterolemia, hypertriglyceridemia, hypo-α-lipoproteinemia, and insulin resistance, all of which are strong proatherogenic risk factors. The mechanisms of PI-induced dyslipidemia are not known but may include inhibition of degradation of ApoB (main Apo of LDL [145]), increased production of VLDL [146], or decreased clearance of LDL as a result of reduced levels of LDL receptor and LDL receptor-related protein [147], blocked adipogenesis and increased lipolysis [148] or stimulation of triglyceride synthesis [149]. Most of these changes are related to "forward" cholesterol transport, enhanced delivery of cholesterol to the cells, including macrophages, in the vessel wall. The SMART study [142, 150] investigated the outcomes of uninterrupted versus interrupted treatment of HIV-infected patients with CART. Treatment interruption normalized CART-induced impairment of lipid metabolism to a large extent but nevertheless, led to increased cardiovascular morbidity and mortality. Thus, CART, using proatherogenic regimens, does increase CAD risk, but treatment interruption does not mitigate or possibly increases this risk even further.

HIV infection and cholesterol metabolism

At a systemic level, disturbances of plasma lipoprotein metabolism associated with HIV infection and immune dysfunction are characterized by increased levels of triglycerides and lowered levels of LDL and HDL cholesterol [151, 152]. These changes in lipoprotein composition, although occurring against a background of low cholesterol, are nevertheless consistent with an atherogenic lipoprotein profile, i.e., a combination of changes in lipid parameters that is usually associated with rapid development of atherosclerosis and a high risk of heart disease. Notably, low levels of HDL and high levels of triglycerides suggest that the RCT branch of cholesterol metabolism may be affected. Consistent with this hypothesis, Falkenbach et al. [153] found clin-

ical and histopathological similarities between AIDS and Tangier disease, a classical disorder of RCT. Recently, it was demonstrated that a decline in HDL levels in treatment-naïve patients correlated with the HIV viral load [154], supporting the direct role of HIV infection in impairment of cholesterol metabolism. HIV-infected patients also have elevated mass and activity of cholesteryl ester transfer protein, resulting in increased transfer of cholesteryl esters from antiatherogenic HDL to proatherogenic LDL [155]. The mechanisms underlying how HIV infection of monocytes and T cells induces systemic effects on lipoprotein metabolism are not known.

A suggestion that HIV affects CAD risk directly was supported further by discovering the mechanisms of the effects of the virus on cellular elements of lipid metabolism. On the cellular level, we have found that HIV blocks reverse cholesterol transport effectively from macrophages by the suppressing ABCA1-dependent pathway and causes accumulation of cholesterol in macrophages [11]. Down-regulation of ABCA1 is mediated by the HIV protein Nef and may be part of the virus' strategy to increase cholesterol content of plasma membrane lipid rafts and assembling virions, resulting in increased viral production and increased infectivity of produced virions (D. Sviridov and M. Bukrinsky, unpublished observation). A side-effect of ABCA1 down-regulation is inhibition of cholesterol efflux and accumulation of cholesterol in HIV-infected macrophages, an effect that may have direct relevance to HIV-related atherosclerosis [11, 156]. Consistent with this idea, examination of atheromatous plaques from HIV-infected individuals by Micheletti et al. [157] demonstrated increased plaque lipid content compared with uninfected donors. Thus, CART and HIV infection itself contribute to pathogenesis of atherosclerosis. Although CART affects mostly forward cholesterol transport (increasing cholesterol delivery to cells), HIV infection impairs reverse cholesterol transport, diminishing cells' ability to remove excessive cholesterol.

CONCLUDING REMARKS

HIV-infected individuals in the developed world now have a significantly reduced risk of AIDS-related death but face HIV-related comorbidities including an increased risk of CAD, the cause of which is potentially multifactorial. The chronic immune activation associated with HIV infection may play an important role in HIV-related CAD pathogenesis. Equally important are the alterations in cholesterol metabolism that can result from HIV infection or specific antiretroviral therapies. Future clinical management of HIV infection will be based on a better understanding of the interplay between the virus, chronic immune activation and inflammation, the activated monocyte and cholesterol metabolism. It is not known whether there is a link among endotoxemia, proinflammatory cytokine production, and CAD risk in individuals on CART who have a suppressed viral load. Addressing these questions will allow informed trials of targeted therapies, such as use of drugs that limit microbial translocation or those that suppress chronic inflammation.

AUTHORSHIP

Clare Westhorpe and Suzanne Crowe are equal, primary authors of this review, performing the majority of the manuscript preparation and editing. Anthony Jaworowski contributed a substantial amount of the text and critical review of the manuscript. Dmitri Sviridov contributed a substantial amount of the text and manuscript editing. Nigora Mukhamedova contributed a substantial amount of the text. Michael Bukrinsky contributed a substantial amount of the text and editing and is co-corresponding author with Suzanne Crowe.

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