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Pathogenesis of AIDS-Related Dilated Cardiomyopathy

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Abstract

The development and application of new more effective antiretroviral therapies and the expanding number of newly diagnosed cases of AIDS have contributed to an overall increase in the number and variety of HIV-related chronic diseases including AIDS related heart disease. AIDS patients have a higher incidence of infectious myocarditis due to their underlying immune deficiencies. However, there is an increasing number of cardiomyopathies of presumable non-infectious origin being reported among HIV-infected individuals. Many heart conditions appearing in AIDS patients resemble chronic dilated cardiomyopathies (DCMs) which are usually seen in older uninfected individuals and suggests that a unique set of risk factors exists for the accelerated development of AIDS-related DCM. Both AIDS-related and non-AIDS-related DCM develop after the triggering of tissue remodeling and reinforcement programs in response to cardiac insult. In AIDS patients with co-existing clinical conditions, e.g. opportunistic infections, nutritional deficiencies, cardiotoxic effects of HAART and illicit drug use provide for a greater variety of external triggers that potentially contribute to the increased heterogeneity of clinical manifestations seen in HIV-related DCM. This review will focus on unique factors that play a role in the etiology of AIDS-related DCM that have evolved along four separate and overlapping pathogenic pathways: interactions between HIV-infected leukocytes and the cardiac microvascular endothelium, viral interactions with cardiac tissues, AIDS-related nutritional deficiencies, and the cardiotoxic effects of therapeutic and illicit drugs.

Key words

Cardiomyopathy. HIV. Metalloproteinase. Cocaine

Introduction

In the absence of pathology, cardiac tissues are integrated in a dynamic relationship with a fibrous collagen extracellular matrix (ECM) that defines and maintains the form and function of the heart. Under normal physiologic conditions, the heart responds to external signals triggered by changes in steady state hemodynamic demands, such as changes in body size or in aerobic activities, by adjusting the composition, phenotype, and intercellular relationships of cardiac tissues and the cardiac ECM, a process called cardiac tissue remodeling[1]. External insults that result in local toxicity and death of cardiac tissues trigger a complex series of interrelated and cascading molecular events that induce pathological reparative remodeling responses, including myocyte hypertrophy and apoptosis, ECM degradation, fibroblast proliferation, and replacement fibrosis[2,3]. The contractile function of the heart is supported by the proper linkage and align-

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ment of cardiac myocytes to the ECM. The degradation of the ECM by matrix metalloproteinases (MMPs) during reparative remodeling results in "myocyte slippage" and thinning or dilatation of the ventricular myocardium[4,5]. This in turn imposes an increased mechanical demand on the heart leading to hypertrophy of the misaligned cardiomyocytes. Inefficient cross-linking of nascent type I and type III fibrillar collagen expressed by proliferating fibroblasts during replacement fibrosis compromises the integrity of the cardiac ECM causing stiffness and reduced heart function, thus contributing to the general pathology of heart disease referred to as dilated cardiomyopathy (DCM).

Since the first cases described by Cohen *et al*[6] in 1986, the number of reports of AIDS related DCM has steadily increased. Estimates based primarily on diagnoses from autopsy results and echocardiography suggest that approximately two thirds of AIDS cases show evidence of cardiovascular disease including DCM during late stage HIV-infection[7]. In non-AIDS-related DCM there exists a large diversity of external stimuli, which target both myocyte and non-myocyte cardiac tissues, that are capable of triggering pathogenic reparative processes characterized by cardiomyocyte hypertophy and matrix remodeling. In the setting of AIDS unique sets of related cardiac insults may occur which can initiate similar pathologic events converging on the common irreversible pathway toward DCM. Although many of the eitological connections remain unclear this review will describe several of the AIDS-related pathologies that may contribute to DCM including AIDS-related leukocyte-endothelial interactions, hormonal-cytokine-growth factor dysregulation, myocarditis, nutritional deficiencies, and related drug cardiotoxicites.

Leukocyte-endothelial interactions

A fundamental connection between AIDS and the immunopathogenesis of DCM is HIV-induced adhesion of leukocytes to the vascular endothelium. Adhesion and transmigration of HIV infected leukocytes into cardiac parenchymal tissues is an initial step in the pathogenesis of immune mediated DCM in AIDS.

Perpherial blood mononuclear cells (PBMCs) infected with HIV demonstrate increased adhesion to primary cultures of vascular endothelial cells in vitro.

HIV infection has been shown to Increase leukocyte adhesion by up regulating cellular adhesion molecules on ECs and on virally infected PBMCs[8-10]. Furthermore, two HIV encoded proteins, the HIV transactivator of transcription (tat) and the 120 kd HIV envelope glycoprotein (gp120), have demonstrated important potentiating effects on vascular endothelial cells and on monocytes in vitro in the absence of HIV infection. HIV-tat induces the expression of IL-1β, IL-6, IL-8, and TNF-α by monocytes[11]. IL-1β and TNF-α, both potent activators of ECs, induce the functional expression of E-Selectin, ICAM-1, and VCAM-1 on vascular endothelial cells. Leukocyte-endothelial interactions also enhance viral infection by promoting HIV replication. Viral replication in monocytes is amplified by EC derived IL-6, IL-1b and MCP-1[8,12]. The potentiation of viral replication creates the opportunity for increased HIV driven leukocyte interactions thus promoting subsequent pathologic events. In addition to leukocyte adhesion, HIV-tat also influences leukocyte transendothelial migration by inducing expression of endothelial cell derived MCP-1 and monocyte MMP9[13,14]. Thus, chemotactic signals and proteolytic enzymes are available to facilitate leukocyte diapedesis into parenchymal tissues where they can trigger pathologic cardiac reparative remodeling processes (see below). Exposure to HIV-gp-120 has recently been shown to induce apoptosis in vascular endothelial cells[15-17]. HIV-gp120 binding to CXCR4 chemokine receptors on cardiac microvascular endothelial cells causes a decrease in the expression of Bcl2 and an increase in the expression of BAX and cytochrome C inducing caspase 3 dependent apoptosis and increased vascular permeability. Thus, the combined effects of HIV-infection, HAV-tat, and HIV-gp120 are increased leukocyte-EC interactions leading to cytokine expression and migration of virally infected leukocytes into cardiac extravascular tissues.

The pathogenic significance of interactions between the cardiac vascular endothelium and HIV-infected leukocytes on the progression towards DCM is related to two aspects of reparative cardiac tissue remodeling: cardiac hypertrophy and cardiac ECM degradation. Under physiological conditions hypertrophy is an adaptive response by terminally differentiated cardiac myocytes to increased hemodynamic demand. Hypertrophic responses to external pressures and mechanical stress are mediated by vasoactive peptides, e.g. AngII and ET-1, and by signaling from the NA^+/H^+ exchanger in cardiac myocytes[18]. However, in addition to mechanical signals, hormones, cytokines, and growth factors expressed during inflammation, viral infection, or pathogenic reparative tissue remodeling can also trigger hypertrophic responses (Table 1). Adult cardiac myocytes are arrested in the G0/G1 phase of the cell cycle and do not undergo mitotic division. Therefore, their response to external growth signals is increased synthesis of contractile proteins (e.g. β-myosin heavy chain and troponin T) and non-contractile proteins (e.g. atrial- and brain-natriuretic peptides), increased fetal gene expression (β-myosin and α-skeletal actin), and increased size (hypertrophy)[19]. Unchecked external trophic signaling can trigger myocyte apoptotic programs. Apoptosis in cardiac myocytes can also be triggered by TNF-α binding to the TNFR1 death receptor[20,21]. TNF-α is upregulated during HIV infection and is expressed by HIV-infected infiltrating leukocytes. These combined effects can all lead to myocyte dropout compromising cardiac contractile function and triggering reparative tissue remodeling.

As mentioned earlier reparative tissue remodeling is a pathologic response that can be triggered by myocyte death, cardiac dysfunction, or pressure overload. In an attempt to balance contractile func-

Table 1. Growth factors that induce hypertrophy in cardiac myocytes in AIDS-related DCM.

Stimulus		Cardiac Tissue Source	Receptor, Transducer Pathway	Ref
Factors				
	FGF	Myocytes, ECM, ECs, SMCs	FGFR, Ras-MEKK1-SEK-JNK	[67;67]
	IGF	Fibroblasts, SMC, ECs	IGFR, Ras-MEKK1-SEK-JNK	[68]
	PDGF	ECs, SMCs	PDGFR, Ras-MEKK1-SEK-JNK	[19]
	TGF	SMCs	TGF Type I/II receptors, Smad proteins	[69]
Cytokines				
	CT-1	Myocytes, fibroblasts	LIFR, gp130-JAK/STAT or gp130-Rac-MEKK-SEK-JNK/SAPK	[70-72]
	IL-6	SMC, ECs	IL6R, Ras-MEKK1-SEK-JNK	[73]
	IL-1β	SMC, EC, fibroblasts, monocyte/macrophages	JAK/STAT or Rac-MEKK-SEK-JNK/SAPK	[74;75]
	TNF-α	cardiac myocytes, SMC, EC, fibroblasts, monocyte/macrophages, T cells	TNFR2 (P75), MAP3K-NFkB	[76;77]
Hormones				
	NE		α1-AR, Gq-PKC-Raf-1; β-AR,Gi-Src-Shc-Grb2-Ras-Raf	[63]
	AT-II	cardiac fibroblasts	AT-IR, JAK/STAT or Raf-MAPKK-MAPK	[69;78;79]
	ET-1	Endothelial cells, Cardiac myocytes, other	ET-A, Ras-MEKK1-SEK-JNK	[67;69;80;81]

Table 2. *Matrix metalloproteinases associated with AIDS-related DCM.*

Common Name	Alternate Names	Substrate Specificities	Disease Association
MMP 1	Collagenase, Fibroblast Collagenase, Interstitial collagenase	Collagen I, II, III, X, gelatin	Idiopathic restrictive DCM
MMP 2	Gelatinase A, Type IV collagenasae, neutrophil gelatinase	Collagen I, IV, V, VII, gelatin, Laminin	Ischemic; DCM
MMP 3	Stromelysin, Transin	Collagen III,IV, V, IX, gelatin, fibronectin, proteoglycans	Ischemic; DCM DCM
MMP 7	Matrilysin, PUMP	Gelatin, fibronectin, proteoglycans	DCM
MMP 9	Gelatinase B	Collagen IV, V, VII, gelatin, proteoglycan, fibronectin, elastin, FAS-L	
MMP 13	Gelatinase 3	Collagen I, II,III	DCM

tion with hemodynamic demand, the collagen ECM in damaged cardiac tissue is degraded by MMPs (Table 2) and repaired by new ECM proteins secreted by cardiac fibroblast and stromal cells[3,5,22,23]. In AIDS these reparative remodeling programs can be compromised. HIV infection induces MMP expression in monocytes. In our laboratory we have measured increased expression of MMP1, MMP2, MMP7, and MMP9 in HIV-infected PBMCs. The combined effect of the coordinated expression of these proteases, which are also found in elevated levels in cases of non-AIDS cardiomyopathy, is accelerated degradation of the cardiac ECM and dilatation of the myocardium. Furthermore, growth factors (e.g. bFGF) which are secreted and bound to heparan sulfate residues on ECM proteins are released and activated by MMP proteolytic cleavage and thus can contribute to myocyte hypertrophy. The significance of chronic exposure to MMPs in the development of DCM has recently been demonstrated in a transgenic mouse model which overexpresses MMP-1[4]. Thus, in the setting of advanced AIDS, HIV-infection and HIV-associated proteins promote leukocyte adhesion and migration through the vascular endothelium, in increased viral replication, increased synthesis of chemokines, cytokines, growth factors, hormones, and MMPs all of which contribute to accelerated reparative cardiac tissue remodeling and DCM.

AIDS-related myocarditis

Experimental infection of non-myocyte cardiac tissues in vitro with HIV has been reported by several laboratories[24,25]. In our own laboratory we have demonstrated that primary cultures of human cardiac microvascular, coronary artery, and aortic endothelial cells are susceptible to both monocytorphic and T cell tropic strains of HIV and SIV[26]. However, detection of HIV infected vascular endothelium in vivo especially in the heart by immunohistochemistry or by molecular in situ hybridization techniques has so far not been convincing; moreover, experimental infection of cardiac myocytes with HIV in vitro has not been successful[27]. Furthermore, despite isolated reports of detection of HIV proviral DNA in myocytes isolated from cardiac tissues from AIDS patients using in situ DNA hybridization or

nested PCR techniques, there is no direct evidence that HIV infection of cardiac myocytes contributes to the pathogenesis of DCM[28,29].

Immunosuppression that occurs during disease progression to advanced AIDS, especially in combination with cocaine abuse, significantly increases the risk for developing active infections with cardiotropic viruses associated with DCM, e.g. coxsackie virus B3 (CVB3) or cytomegalovirus (CMV)[30-33]. Reactivation of CMV can also induce immunosuppression and thus compound the risk for viral myocarditis and DCM[34]. The enteroviruses, especially CVB3, are the most common viruses associated with viral cardiomyopathies[31]. It has been demonstrated that CVB infection leads to cardiac myocyte cell death in vitro[35,36]. In vivo this would correspond to cardiac myocyte dropout and the initiation of reparative tissue remodeling leading to DCM. In vivo viral infections of the heart have also been shown to cause auto-immune myocarditis in experimental animal models[37]. In CVB3 infections in mice, pathogenic autoimmune responses triggered by antigenic mimicry are characterized by detection of heart specific autoantibodies, and heart infiltrating auto-reactive cytotoxic T cells[38]. Cytokines e.g. TNF-α also contribute to decreased myocyte function, cardiotoxicity, and myocyte drop out[39]. Mice immunized with murine cardiac myosin in the absence of viral infection develop autoimmune myocarditis similar to CVB3 infected mice[40]. Thus, in addition to direct killing of infected cardiac myocytes cardiotropic viruses such as CVB3 can contribute to the development of DCM by triggering pathological cardiac specific autoimmune responses.

However, the role such virally mediated immunopathological pathways may play in the setting of immunosuppression in advanced AIDS is unclear. Recently, a molecular basis for a causal relationship between CVB infection and DCM was described[31,41,42]. CVB encodes an enzyme, protease 2A, that specifically cleaves the cytoskeletal protein dystrophin at its hinge 3 region causing the disruption of the cardiac sarcogylcan complex. This effectively dissociates the cardiac myocyte from its tethered relationship to the cardiac ECM resulting in myocyte slippage and the progression towards DCM. This same DCM is seen in subjects with Duchenne and Becker muscular dystrophies which are characterized by a common genetic mutation in the gene encoding dystrophin. According to one study, enteroviral-specific nucleotide sequences have been detected in approximately 30% of patients with lymphocytic myocarditis and DCM[30]. Thus, viral infection of the heart can lead to AIDS-related DCM by disrupting the functional relationship of cardiac myocytes to the cardiac ECM, by directly killing infected cardiac myocytes, and by inducing myocyte-directed auto-immune responses.

AIDS-related nutritional deficiencies

Nutritional deficiencies associated with AIDS are caused both by malabsorption in the gut and by depletion of micronutrients during virus infection and replication. Deficiencies in micronutrients including selenium, β-carotene, vitamins A & E, the B vitamins, zinc, and magnesium have all been documented in the disease progression to AIDS and have been associated with increased oxidative stress and with defective T cell function[43-46]. Among these, selenium deficiency is of greatest significance in the pathogenesis of AIDS-related cardiomyopathy[47-49]. Selenium deficiency has been identified as the primary cause of Keshan disease, a dietary related form of dilated congestive cardiomyopathy. Selenium is also a co-factor for glutathione peroxidase, an important cellular antioxidant. Decreased levels of selenium that occur with disease progression to late stage AIDS are associated with an accumulation of reactive oxygen species (ROS) and an overall increase in the levels of oxidative stress within the heart[5,46,48]. This in turn interferes with the physiological regulation of intracellular Ca^{+} and the activity of the cardiac sarcolemmal NA^{+}/H^{+} exchanger causing cardiac myocyte dysfunction and contributing to the development of DCM[50,51].

Selenium is also involved in attenuating toxic levels of proinflammatory cytokines which occur in advanced AIDS. During late-stage HIV infections, systemic levels of TNFα and IFN-γ increase due to chronic inflammation contributing to wasting and malabsorption of micronutrients. Elevated levels of TNF-α also promote an increase in HIV viral replication by activation of the NF-κB pathway thus perpetuating HIV-antigen driven inflammation. Elevated levels of TNF-α also cause myocyte dysfunction and death[52]. Selenium inhibits TNF-α mediated HIV replication[53] and modulates the pathogenic effects of TNF-α by down-regulating expression of TNF type II receptors[54]. Thus selenium (as well as other AIDS-sensitive micronutrients, e.g. vitamin E) plays a critical role in preventing the development of DCM by promoting proper immune function, attenuating oxidative stress, controlling HIV replication, and ameliorating the adverse effects of proinflammatory cytokines.

AIDS related nutritional deficiencies also contribute to the pathogenesis of viral myocarditis. The traditional view has assigned the deleterious effects that AIDS-related nutritional deficiencies may impose on host immune function as the reason for increased susceptibility to infection with cardiotropic viruses, e.g. CVB3. However, the effects of a nutritionally restricted environment on virus replication and the determination of pathogenic phenotypes has not been examined. Recently, Melinda Beck has described a relationship between micronutrients, antioxidants, and the determination of virulent genotypes of CVB in mice[4,52,55,56]. Experimental mice were maintained on a selenium deficient diet and control mice were fed a normal diet. After four weeks both groups were injected with an avirulent virus strain, CVB3/0 which replicates in the heart but does not cause detectable disease. Within 10 days the selenium deficient mice developed obvious myocarditis while control mice were disease free. When virus was isolated from the experimental

group and introduced into the healthy controls, they developed viral myocarditis, suggesting that the disease was related to a change in viral phenotype as opposed to a nutritionally weakened host immune response.

Selenium is involved in the synthesis of a variety of proteins, however, as a cofactor for the antioxidant glutathione peroxidase, selenium plays an important role in regulating oxidative stress. Glutathione peroxidase activity in mice fed selenium deficient diets was only 20% of that measured in the control group. Therefore, to determine if the observed effect of selenium on the selection of viral pathogenic phenotypes was related to oxidative stress, glutathione peroxidase knockout mice and control mice were injected with the CVB3/0 strain. Again, after ten days all of the control mice were disease free. However, greater than 50% of the knockout mice developed viral myocarditis. Sequence analysis of the genomes of virus isolated from mice that had developed myocarditis and from healthy controls revealed that a mutation involving 7 nucleotides was consistently found in the knockout mice with myocarditis. Furthermore, essentially the same mutations were seen in viruses isolated from the selenium deficient mice with myocarditis. These results demonstrate that nutritionally-related oxidative stress in the setting of AIDS may play a deterministic role in the development of viral myocarditis related to DCM.

AIDS-related drug effects

Highly active antiretroviral therapy (HAART) is a multi-drug therapy that combines protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs) to limit HIV viral replication in AIDS patients. Among these antiretroviral therapeutic agents, NRTIs are more closely associated with AIDS-related DCM. Cardiac myocytes contain the highest density of mitochondria of any cell in the body, presumably because of their increased requirement for ATP energy production. It is thought that NRTI cardiotoxicity is related to detrimental effects on cardiac mitochondrial function. NRTI's like zidovudine (3'-azido-3'-deoxythymidine [AZT]) enter infected cells where they become phosphorylated and behave as competitive inhibitors of viral reverse transcriptase. AZT triphosphate has a much greater affinity for viral RT than for human cellular DNA polymerase (α, β, δ, and ε). However, phosphorylated forms of AZT and other commonly prescribed NRTIs, such as ddC and d4T, are able to inhibit human DNA polymerase γ, which is exclusive to the mitochondrial matrix and involved in mtDNA synthesis[57]. Results of several studies indicate that NRTIs may have both short term and long term negative side effects on cardiac mitochondrial function[4,52,55,56,58,59]. In the short term NRTIs exert adverse cellular changes e.g. accumulation of ROS that affect the respiratory chain and reduce energy production; in the long term mtDNA replication and protein synthesis are compromised leading to mitochondrial and ultimately myocyte dysfunction. Despite some reports of the negative effects of zidovudine on cardiac dysfunction and on the development of cardiomyopathy in murine models[59,60], questions remain regarding the specific mechanisms and tissue specific responses to AZT involved in humans.

Effects of HIV infection and cocaine abuse

Left ventricular hypertrophy and DCM have been described as myocardial manifestations of chronic cocaine abuse in both human cases and in animal studies[61-64]. The cocaine-induced catecholamine, NE, has been shown to induce hypertrophic changes in neonatal cardiac myocytes cultured in the absence of mechanical stress[63]. Catecholamines can also trigger the synthesis and expression of extracellular matrix proteins by fibroblasts. However, the complicated pathogenic mechanisms involved in the development of DCM in the setting of cocaine abuse and advanced AIDS have not been elucidated.

In vitro studies have demonstrated that HIV infection increases the adhesion of monocytes to human umbilical vein endothelial cells in vitro. Our laboratory has recently studied the combined effects of HIV infection and NE on leukocyte-endothelial interactions. For these studies matched sets of autologous human cardiac microvascular endothelial cells and HIV-infected PBMCs were placed in coculture for 48 hours. A dose dependent enhancement in leukocyte adhesion was measured under both static and flow conditions after the addition of NE. NE significantly increased adhesion of both infected and uninfected PBMCs relative to untreated controls. MMP activities were also measured under the same culture conditions. Interaction of HIV-infected PBMCs with HMVEC-Cs resulted in increased detectable levels of activity in MMP1, MMP2, MMP7, and MMP9, as well as increased surface expression of CD147 or extracellular matrix metalloproteinase inducer (emmprin)[65,66] on infected PBMCs. MMP activity was not detected in cocultures with uninfected PBMCs. However, addition of NE in coculture induced MMP activitity in uninfected cocultures and enhanced the active levels of MMP1, MMP2, MMP7, and MMP9 in cocultures with HIV-infected PBMCs. The potentiating effects of NE and HIV infection on leukocyte interactions with HMVEC-Cs and on MMP expression support a role for the combined effects of HIVinfection and cocaine-induced catecholamines in the pathogenesis of AIDS-related DCM.

Summary

In this review DCM has been described as the clinical manifestation of chronic pathological cardiac reparative tissue remodeling occurring in both AIDS-related and non-AIDS-related heart disease. Three defining characteristics of DCM include, cardiac myocyte hypertrophy-deathand dropout,

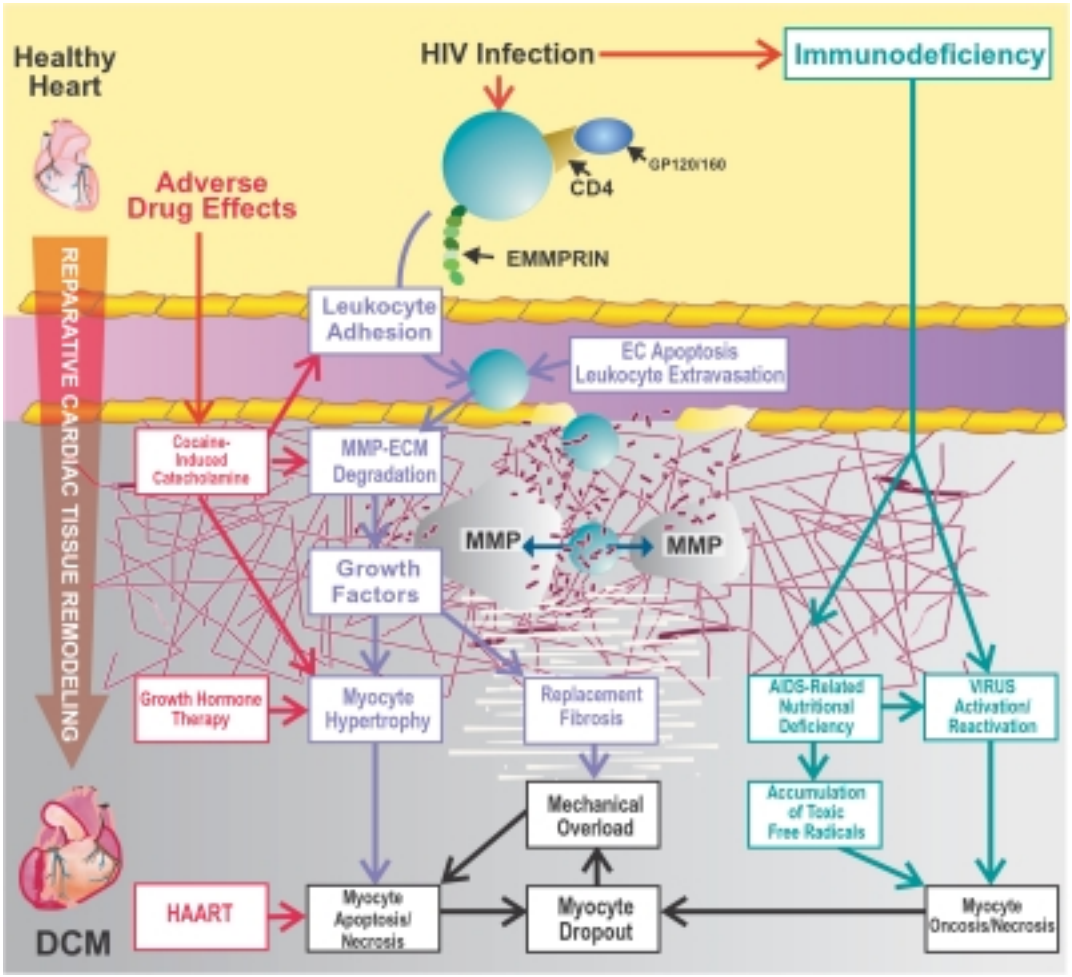

Fig. 1. *Proposed model for overlapping pathogenic pathways in the development of AIDS-related dilated cardiomyopathy.*

degradation of ECM proteins by MMPs, and reparative replacement fibrosis. These three inter-related processes are triggered by external stimuli and lead to pathological modifications in the geometry and function of the heart which are characterized by ventricular dilatation and decreased cardiac output. AIDS and AIDS-related co-morbid conditions, present a unique set of cascading events that are related to one or more of these three processes and that contribute to an accelerated progression towards DCM (Fig. 1). HIV infection has a direct potentiating effect on leukocyte interactions with cardiovascular tissues leading to ECM degradation, myocyte hypertrophy, and replacement fibrosis. HIV-induced nutritional and immunodeficiencies promote the accumulation of cardiotoxic ROS and increased susceptibility for infection with and/or reactivation of cardiotropic viruses, e.g. CVB3 and CMV. Antiviral drug therapies and illicit drug abuse can synergize with the HIV-mediated enhancement of leukocyte-cardiovascular interactions and promote ECM degradation and myocyte hypertrophy and death. This abbreviated representation of the complex clinical picture of HIV-related DCM may highlight some of the important future considerations for research and therapy for heart disease in the setting of AIDS.

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