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HIV and SIV Associated Thrombocytopenia: An Expanding Role for Platelets in the Pathogenesis of HIV

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Abstract

Thrombocytopenia is common in HIV and SIV infection, and is often associated with disease progression. HIV and SIV-associated thrombocytopenia arise through multiple mechanisms, including decreased platelet production, increased platelet destruction due to HIV-mimetic anti-platelet antibodies, and increased use of activated platelets. Activated platelets have the potential to contribute to the pathogenesis of HIV and SIV by interacting directly with inflammatory cells and endothelium and by releasing soluble immunomodulatory cytokines.

Introduction

The lentivirus human immunodeficiency virus (HIV) is responsible for acquired immune deficiency syndrome (AIDS) and the deaths of 24 million people world-wide.[1] HIV targets cells expressing the receptors CXCR4 or CCR5, disease progression is characterized by the depletion of CD4+ T cells, and mortality generally results from opportunistic infections secondary to immunosuppression.[2] Progression can be slowed with combination anti-retroviral therapy (cART).[3] Simian immunodeficiency virus (SIV) is closely related to HIV and causes AIDS-like symptoms in infected macaques, thus serving as the premier animal model to study the pathogenesis and treatment of HIV.[4]

Prior to the discovery of HIV as the cause of AIDS, a role for platelets in the pathogenesis of the disease was postulated due to the recognition of platelet decline as a symptom of disease. [5] Platelets are small, anucleate blood cells that originate as evaginations from bone marrow megakaryocytes. Though best known as cellular coordinators of hemostasis, participation of the platelet in the immune response to bacteria, parasites, and viruses is increasingly being recognized and reported in the literature.[6]

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Thrombocytopenia in HIV

Thrombocytopenia is defined by a low blood platelet count of $<100 \times 10^9/L$, with a count $<50 \times 10^9/L$ considered severe and $<10 \times 10^9/L$ considered at risk for spontaneous bleeding. A recent meta-analysis reviewing thrombocytopenia in HIV-infected individuals prior to cART concluded that the prevalence of HIV-associated thrombocytopenia (HAT) is 5–30%,[7] but this figure has improved since the advent of cART (see below). A recent large survey of cART-treated HIV-infected individuals reported a prevalence of HAT of 3.2%.[8] Furthermore, 22% of adults diagnosed with immune thrombocytopenia are HIV-positive,[9] and therefore HIV infection should be considered as a differential diagnosis for individuals presenting with thrombocytopenia.

Direct involvement of platelets in the pathogenesis of HIV is implied by multiple reports of associations between alterations in platelet count (or platelet activation markers) and HIV disease progression. Platelet count has been inversely correlated with plasma viral load in both untreated HIV+ individuals[10] and in SIV-infected pigtailed macaques,[11] and a decrease in platelet number predicted a steep decline of CD4+ T cell counts in homosexual men.[12] AIDS patients have an increased frequency of thrombocytopenia when compared with asymptomatic HIV+ individuals. One study found that 21.2% of AIDS patients had thrombocytopenia compared to 9.2% of asymptomatic patients,[13] while another large-scale review found 8.7% of AIDS patients have thrombocytopenia compared to 1.7% of asymptomatic individuals.[14] Severe thrombocytopenia, most often associated with the acute phase of HIV infection, carried less positive predictive value than moderate to mild thrombocytopenia for the development of AIDS in a large group of HIV+ patients.[15] Further, our group has demonstrated that the magnitude of platelet decline during chronic HIV infection and during chronic SIV infection is predictive for the later development of HIV or SIV-induced CNS disease.[16,17]

Thrombocytopenia has been identified as a strong independent predictor for mortality in both untreated HIV+ patients and SIV-infected pigtailed macaques.[11,18] Conversely, an elevated platelet count (thrombocytosis) has been associated with an increased risk of AIDS and death in HIV-infected hemophiliacs,[19] and may indicate a different role for the platelet in the pathogenesis of HIV in this subset of patients. Indeed, the presence of thrombocytosis may be detrimental in some cases, and has also been correlated with immune reconstitution inflammatory syndrome (IRIS) [20] and an increased risk for HIV-associated cardiovascular disease.[21] Regardless of their negative or positive nature, the existence of multiple reports of correlations between platelet count and outcome measures implies that platelets play a critical role in the pathogenesis of HIV infection.

In general, HAT has not been associated with coagulation deficits. Historically, incidence of bleeding has been correlated with the severity of the platelet deficit, and up to 40% of severely thrombocytopenic HIV+ individuals experienced bleeding.[13] However, a pre-cART report of bleeding in 1–2% of individuals with HAT[22] is small compared to a recent report of a 17.8% prevalence of HAT-associated bleeding in cART-treated patients,[8] indicating that cART use alters the nature of the observed thrombocytopenia. HAT in the latter study was additionally associated with hepatitis C virus co-infection and hepatic cirrhosis, indicating that the bleeding events may have arisen secondary to a clotting factor deficiency in addition to a decreased number of platelets.

It is also likely that the etiology of HAT varies with the phase of infection. The pattern of HAT is biphasic in nature, with a transient initial drop during acute infection followed by a less marked decline that persists during chronic infection.[15,17] An examination of the kinetics of HAT in humans demonstrated that both a decrease in platelet production and a

decrease in platelet lifespan contribute to HAT.[23] A decrease in platelet lifespan has been noted in the absence of decreased production, in the presence of an increased megakaryocyte pool within the bone marrow,[24] and in non-thrombocytopenic individuals.[25]

Defining the complex causes of decreased platelet production is complicated by variable disease progression in HIV-infected humans. For example, variations in the timing of megakaryocyte exposure to HIV may explain conflicting studies that report either a paucity[26] or excess[27] of megakaryocytes in the bone marrow of individuals with HAT, with either increased or decreased colony formation by megakaryocytes *in vitro*. [28] Studies have demonstrated that HIV-1 envelope protein gp120 is sufficient to cause apoptosis of CD34+ megakaryocyte progenitor cells in culture, thereby reducing platelet production.[29] In contrast, apoptotic mechanisms in mature megakaryocytes normally contribute to platelet production.[30] HIV-induced apoptosis of platelet progenitors within the bone marrow is therefore a complex influence on platelet number.

Alternatively, megakaryocyte malfunction secondary to inflammatory cytokine stimulus may adversely affect thrombopoiesis. Abnormal megakaryocyte morphology has been noted in multiple reports (example in Abgrall 1992),[28] and thrombopoietin, a potent stimulus for thrombopoiesis that is negatively regulated by platelet uptake from the circulation and therefore normally rises with platelet decline, is elevated in HIV-infected individuals yet is not correlated with platelet number.[31] It has been previously reported that resting bone marrow macrophages release soluble cytokines that promote megakaryocyte growth and platelet release while LPS-activated macrophages inhibit megakaryocyte development and growth,[32] but a similar inhibitory role for activated or infected bone marrow macrophages in the context of HIV has yet to be explored.

Increased platelet destruction due to an autoimmune etiology offers an explanation for the decreased lifespan of platelets that is observed in the context of HAT, and a similarity of HAT with immunologic thrombocytopenic purpura (ITP) has been commented upon by multiple authors (as reviewed by Liebmann 2007).[7] Platelets from some patients affected by HAT or ITP share similar kinetics characterized by a decreased platelet lifespan in the presence of an expanded megakaryocyte compartment within the bone marrow,[27] and undergo phagocytosis by splenic macrophages at a high frequency.[33] A plethora of different anti-platelet antibodies and immune complexes have been detected in sera from HIV+ individuals, and many of these antibodies cross-react with glycoproteins on HIV's viral envelope (Table 1).

Platelet count is inversely correlated with the level of anti-platelet IgG in HAT,[34] and anti-GP IIIa aa49-66 has been shown to cause platelet fragmentation through the induction of peroxide in a complement independent manner.[35] HIV's mimicry of host glycoproteins therefore directly contributes to platelet decline.

A Role for the Activated Platelet in the Pathogenesis of HAT and HIV

An alternative explanation for the shortened platelet lifespan observed in HIV-infected individuals is platelet activation and subsequent clearance of activated platelets from the circulation.[30] Platelet activation has long been proposed as a cause of thromboembolic sequelae of HIV infection. With a prevalence ranging from 0.26–7.6% in the HIV+ population, thromboembolic events are relatively common in HIV-infected individuals.[36] The risk for deep vein thromboses alone is 4–10 times that of the normal population.[37,38] Some thromboembolic events, such as pulmonary arterial hypertension and deep vein thromboses, are associated with normal to elevated platelet counts, while others, such as thrombotic microangiopathy, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, correlate with a thrombocytopenic state. Thrombotic microangiopathy has also

been reported in HIV-2 infected pigtailed macaques,[39] and inoculation of rhesus macaques with chimeric simian-human immunodeficiency virus containing HIV-*nef* is associated with an increased incidence of pulmonary arterial hypertension.[40] The pathogenesis of this wide range of thromboembolic events is not yet fully defined, but the presence of platelet activation could contribute.

Platelet activation is measured by the release or expression of specific factors. Platelets are translationally active, synthesize a milieu of inflammatory and other cytokines for storage in dense and alpha granules, and can respond to physical and chemical stimuli by releasing these factors into the environment and differentially regulating surface expression of receptors through fusion of storage granules with the plasma membrane (reviewed by Ombrello 2010 and Semple 2011).[41,42] Surface markers are the most specific indicators of platelet activation, and are upregulated in HIV-infected individuals. In one survey of 20 HIV-infected individuals with normal platelet counts, an increase in both surface p-selectin and CD63 was noted; further, the increase in p-selectin was more pronounced in patients with AIDS.[43] Another study of 17 AIDS patients corroborated these earlier findings by also revealing elevated CD63 (p-selectin was not measured).[44] Both p-selectin and the integrin CD63 mediate the adhesion of platelets to endothelium and inflammatory cells, and may help to directly activate these bound cells or allow for targeted delivery of soluble factors that are concurrently released during platelet activation.

Soluble markers of platelet activation are less specific, as artifactual release during phlebotomy may contaminate serum samples and many of these factors also may be released by either activated endothelial cells or monocytes. One potential solution to this problem is to examine platelets from HIV-infected individuals *in vitro* for their responsiveness to a variety of stimuli rather than measuring inflammatory factors within the collected serum. Such a study design revealed an enhanced propensity of platelets from HIV-infected individuals to release the cytokine “Regulated upon Activation Normal T-cell Expressed and Secreted” (RANTES/CCL5).[43] This supports reported elevations of serum RANTES/CCL5 in HIV+ individuals at varying stages of disease[45] and in patients on antiretroviral therapy[46] despite any impact of platelet processing technique on measured levels.[47] Interestingly, pre-incubation of platelets with HIV gp41 enhances their release of RANTES but not platelet factor 4 (pf4) upon stimulation by the SFLLRN thrombin receptor agonist peptide.[48] RANTES has the potential to compete with HIV for binding with CCR5, thereby potentially inhibiting the spread of infection.

Many other soluble markers of platelet activation also have the potential to play a significant role in the immune response to HIV. Reports conflict as to whether soluble CD40L (sCD40L) is increased in serum, with one study finding a 1.5 fold elevation in infected individuals compared to controls,[46] a second finding no difference,[49] and a third finding a correlation of sCD40L level with CNS disease.[50] HIV *tat* directly stimulates the release of platelet sCD40L in a CCR3 and β 3-integrin dependent manner,[51] resulting in enhanced B cell activity, upregulation of MCP-1 and IL8 within endothelial cells,[52] and release of TNF α , IL-1 and IL-6 from monocytes.[53] MCP-1 is also elevated in the serum of HIV-infected individuals[49] and cerebral spinal fluid of SIV-infected macaques. MCP-1 acts as a potent chemoattractant for monocytes and has been implicated in the pathogenesis of SIV-associated CNS disease.[54] Though multiple cells within the CNS are thought to act as a source for MCP-1, brain microvascular endothelial cells and the platelets bound to them also may serve as a local source of this chemokine and therefore guide other inflammatory cells to sites of inflammation. Though generalized elevations of platelet factor 4 (pf4) in HIV infection have yet to be characterized, pf4 may originate from activated platelets or monocytes, acts as a trigger of monocyte to macrophage switching,[55] and enhances HIV-1 replication in macrophages *in vitro*. [56] sCD40L, MCP-1 and pf4 are all stored within

platelet alpha granules. The regulatory mechanisms that allow some but not all of these factors to be elevated in the context of HIV-infection remain to be elucidated. These may include regulated production at the level of translation, specific receptor-mediated uptake of some factors but not others, and the establishment of distinct subsets of alpha-granules or platelet populations.

Platelets may contribute directly to the pathogenesis of HIV by aiding viral replication and distribution. Megakaryocytes within the bone marrow express HIV's receptor and co-receptor for cell entry, CD4+ and CXCR4+, respectively.[57] Megakaryocytes can be productively infected with HIV *in vitro* and *in vivo*,[58,59] and may serve as a reservoir for latent virus. Additionally, platelets, though lacking CD4+ expression, continue to express CXCR4,[60] and an increase in platelet microparticles has been noted in HIV-infected individuals.[61] CXCR4+ microparticles can fuse with CD4+ CXCR4 null cells and, as a result, create novel targets for productive HIV infection.[62] Though platelet concentrates and alpha granule contents have virucidal properties,[63] circulating platelets can alternatively endocytose HIV through DC-SIGN and CLEC-2 binding, store the intact viral particles in protected endocytic vesicles,[64] and may therefore deliver infective HIV to distant organs.

The Effect of Antiretroviral Therapy on Platelets

Many commonly used antiviral drugs affect platelet count and activation. cART alone is often sufficient to correct thrombocytopenia, and the development of recurring thrombocytopenia upon cART discontinuation in some patients further strengthens the correlation.[65] The ability of the nucleoside analog reverse transcriptase inhibitor (NRTI) azidothymidine (AZT, Zidovudine) to affect platelet number has been extensively studied alone and in cART: between 24–34% of HAT patients undergo a complete recovery of platelet number with AZT, and an additional 33–44% demonstrate a partial response.[66,67] Unfortunately, this response tends to be transient in nature even with increasing doses,[68] and AZT is reported to produce myelodysplastic syndrome with thrombocytopenia in mice. [69] 2',3'-dideoxyinosine (ddI, Didanosine), another NRTI, is associated with a sustained increase in platelet number in patients with HAT, but is also associated with side effects such as peripheral neuropathy, diarrhea and pancreatitis.[70] 2',3'-dideoxycytidine (ddC, Zalcitabine) does not affect platelet number alone,[71] but in concert with AZT was successful in restoring a normal platelet count in one patient who had been refractory to treatment with intravenous immunoglobulin therapy (IVIg, see below).[72] Protease inhibitors (PI) in general are associated with an increased rate of thromboses[73] and their use is correlated with increased surface expression of platelet CD40L,[74] yet individual PIs such as ritonavir and indinavir are associated with an increased risk of abnormal bleeding events,[75] and tipranavir-ritonavir therapy decreases platelet aggregation and thromboxane B2 concentration in activated platelet rich plasma.[76]

If cART fails to correct thrombocytopenia in the symptomatic patient, more traditional therapies such as corticosteroids, intravenous immunoglobulins, anti-Rh (anti-D) and splenectomy may be considered.[77] Though direct stimulation of platelet production through treatment with recombinant thrombopoietin (PEGHuMGDF) in HIV-infected chimpanzees was overwhelmingly successful in increasing platelet number tenfold, increasing the bone marrow megakaryocyte compartment thirtyfold and decreasing anti-GPIIIa 49–66 antibody,[78] such therapy is contraindicated because it was associated with the formation of anti-thrombopoietin antibodies in healthy individuals during clinical trials. [79] Romiplostim, a novel thrombopoietin mimetic, outperformed standard of care treatments with a high rate of platelet increase and low incidence of treatment failure in one

study of 157 patients with immune thrombocytopenia,[80] but its therapeutic potential has yet to be evaluated in the context of HIV infection.

Therapeutics for common HIV-associated opportunistic infections and other sequelae also may affect platelets. Megestrol acetate is commonly used for the treatment of HIV-associated anorexia-cachexia and is associated with increased platelet count and survival. Though it does not decrease the level of anti-platelet IgG, it decreases monocyte recognition of platelet-associated IgG.[81] Diamino-diphenylsulfone (Dapsone) is used to treat opportunistic infections with *Pneumocystis jirovecii* and *Toxoplasma gondii*, and has been associated with recovery of platelet number in approximately 50% of HAT patients with elevated anti-platelet IgG.[82,83] Conversely, the antibiotic rifampin is used to treat *Mycobacterium avium*, and has been shown to cause a reversible thrombocytopenia in both uninfected and HIV-infected individuals.[84] Valproic acid is a mood stabilizing histone deacetylase inhibitor that is associated with decreased levels of serum sCD40L in HIV+ individuals; it also inhibits the release of sCD40L and pf4 from HIV-*tat* stimulated platelets in a mouse model.[85] A number of platelet activating factor (PAF) antagonists inhibit HIV reverse transcriptase activity[86] and may prevent PAF-mediated neuronal apoptosis in HIV-associated CNS Disease; since the apoptosis is mediated through the NMDA receptor,[87] and megakaryocytes also express NMDA receptors and undergo apoptotic change in the context of HIV infection,[88] PAF antagonists may show additional utility in the maintenance of the megakaryocyte compartment within the bone marrow. Interestingly, though statin and fibrate treatments for the management of high cholesterol usually target and decrease platelet activation, in HIV-infected individuals both pravastatin and fenofibrate fail to decrease serum p-selectin levels.[89]

Summary and Conclusions

Thrombocytopenia is common in HIV infection, and is often associated with adverse sequelae. Thrombocytopenia arises through multiple mechanisms (Figure 1), including decreased platelet production, increased platelet destruction due to HIV-mimetic anti-platelet antibodies, and increased use of activated platelets. Activated platelets have the potential to contribute to the pathogenesis of HIV by interacting directly with inflammatory cells and endothelium, by releasing immunomodulating cytokines and by harboring infective viral particles within the blood.

cART is often sufficient to correct HAT, and a number of reports of therapeutics that affect both platelet function and HIV pathogenesis may reveal a new strategy in the search for novel antiretroviral drugs. For example, dipyridamole (DPM) is a coronary vasodilator and inhibitor of platelet aggregation, and has been shown to potentiate the inhibitory effects of AZT and ddC on HIV replication in macrophages in vitro while not potentiating the myelotoxic effects of AZT.[90] Additionally, two of the compounds isolated from the herb *Artemisia capillaries* were able to inhibit both platelet aggregation and HIV replication.[91] Further cross-referencing of the pharmacology literature on the development of therapeutics for HIV and platelet dysregulation may reveal additional potential treatments.

Future studies of the role of the platelet in the pathogenesis of HIV should take into consideration the nature of both HIV and the platelet in order to better understand their relationship. As there is likely a continuum of varied mechanisms that contribute to thrombocytopenia throughout the course of HIV infection, consideration of disease stage and past and present treatment status is likely to better demonstrate the relationship between platelet activation and disease outcome. The use of the SIV-infected macaque model will help elucidate the role of the platelet in the innate immune response during acute infection. Because of the excitable nature of the platelet, multiple measures of platelet activation

should be examined. A careful review of the platelet presentome and secretome in the context of the phase of HIV infection may reveal intricacies of differential platelet factor regulation. The role of activated platelets in the pathogenesis of HIV warrants further study and a better understanding of the platelet's contribution may lead to novel therapies for HIV.

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Figure 1.

HIV-Associated Thrombocytopenia (HAT) arises through multiple mechanisms, including increased destruction, increased activation, and decreased production, that have the potential to contribute to the pathogenesis of HIV infection.

Table 1

Molecular Mimicry Plays a Role in Autoimmune Destruction of Platelets in HAT: Antibodies versus HIV glycoproteins cross-react with platelet glycoproteins on the host platelet's surface

Platelet Surface Glycoprotein	HIV Protein	Reference
GP Ib/IX	gp160	Kaplan 1996[92]
GP IIb/IIIa	gp120	Bettaieb 1996[93]
GP IIIa	gp41	Wiwanitkit 2008[94]
GP IIIa aa49-66	nef	Li 2005[95]
GP IIIa aa749-761	gp41	Dominguez 1998[96]
Platelets (antigen unknown)	p24	Hohmann 1993[97]