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TOPIC HIGHLIGHT

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Effects of human immunodeficiency virus on the erythrocyte and megakaryocyte lineages

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Abstract

Anaemia and thrombocytopenia are haematological disorders that can be detected in many human immunodeficiency virus (HIV)-positive patients during the development of HIV infection. The progressive decline of erythrocytes and platelets plays an important role both in HIV disease progression and in the clinical and therapeutic management of HIV-positive patients. HIV-dependent impairment of the megakaryocyte and erythrocyte lineages is multifactorial and particularly affects survival, proliferation and differentiation of bone marrow (BM) CD34+ haematopoietic progenitor cells, the activity of BM stromal cells and the regulation of cytokine networks. In this review, we analyse the major HIV-related mechanisms that are involved in the genesis and development of the anaemia and thrombocytopenia observed in HIV positive patients.

Key words: Human immunodeficiency virus; Erythrocytes; Megakaryocytes; Haematopoietic progenitor cells; Virology

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INTRODUCTION

Human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS), which is characterised by the progressive and fatal impairment of immune system function and the occurrence of opportunistic infections and tumours[1]. Although the dysfunction of the immune system and the decline in the number and activity of CD4+ T cells represent the hallmark of HIV infection, it is noteworthy that HIV can also interfere with other cell lineages and tissues[2-5]. In addition to progressive depletion of CD4+ T lymphocytes, peripheral blood cytopenias, such as anaemia, neutropenia and thrombocytopenia, occur in most patients with AIDS[6,7] and in some HIV-positive naive individuals during the early phases of disease progression, especially when high plasma levels of HIV RNA are detectable. Interestingly, isolated thrombocytopenia can represent the first clinical manifestation in otherwise asymptomatic HIV positive patients[8] whereas anaemia and neutropenia are more common in the late stages of

HIV disease[9]. These peripheral blood cytopenias have been observed even in the absence of tumours, chemotherapeutic treatment or opportunistic infections suggesting that HIV infection may be directly associated with the induction of these haematological abnormalities[10]. The progressive depletion of these cell lineages in the blood has been related to several HIV-driven mechanisms: (1) the impairment of survival and proliferation of haematopoietic progenitor cells (HPCs); (2) the inhibition of the differentiation of HPCs into certain cell lineages or direct action on mature cells; (3) the impairment of stromal cells; and (4) the dysregulation of cytokine production and the appearance of autoimmune responses. In this report, we analyse several aspects of these major HIV-related mechanisms that are involved in the impairment of the erythrocyte and megakaryocyte (MK) lineages.

HIV AND CD34+ HPCs

The bone marrow (BM) forms a suitable environment for stem cell survival, growth and differentiation. The cellular components of BM include HPCs, HPC-derived cell lineages and stromal cells. HPCs represent a heterogeneous CD34+ cell population in the BM that includes the most primitive CD34+ haematopoietic stem cells (HSCs), which are characterised by pluripotency and a high capacity for self-renewal, and the CD34+ multi-potent progenitors (MPPs), which originate from HSCs and are multipotent but have a more limited capacity for self-renewal (Figure 1). MPPs can differentiate into common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs). CLPs can differentiate into B and T cells, natural killer cells and plasmacytoid dendritic progenitor cells. T cell differentiation occurs in the thymus whereas CMPs differentiate in the BM, through specific differentiation stages, into several cell lineages including granulocytes, erythrocytes, MKs and monocytes[11]. CMP-derived cell lineages migrate into the blood with the exception of MKs, which are maintained in the BM. The differentiation of HSCs is regulated by specific haematopoietic growth factors that induce the survival, proliferation and maturation of specific cell lineages. These factors share several common properties and act hierarchically at different stages of differentiation, and they often show synergistic or additive interactions with other growth factors. Stromal cells are the major source of these factors with the exceptions of erythropoietin (EPO) and thrombopoietin (TPO), which are largely produced in the kidneys and the liver, respectively.

The incidence of peripheral blood cytopenias in HIV positive individuals has led to hypothesis that HIV can impair BM homeostasis and affect the biology and activity of HPCs. Early studies have observed that HIV infection is correlated with the depletion of HPCs and a significant reduction in the *in vitro* growth of HPCs that have been purified from HIV-infected patients[12-17], suggesting that the multiple peripheral cytopenias may be related, at least in part, to a productive HIV infection of

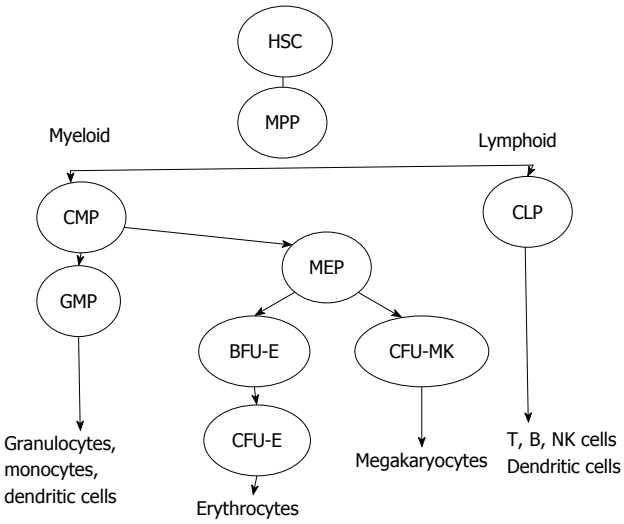

Figure 1 Human haematopoiesis. HSC: Hematopoietic stem cell; MPP: Multipotent progenitor; CLP: Common lymphoid progenitor; CMP: Common myeloid progenitor; GMP: Granulocyte/macrophage progenitor; MEP: Megakaryocyte/erithrocyte progenitor; BFU-E: Burst forming unit-erythroid; CFU-E: Colony forming unit-erythroid; CFU-MK: Colony forming unit-megakaryocyte.

BM HPCs. HIV infection may determine a progressive HPC depletion due to cell lysis, which in turn leads to the derangement of the differentiation towards various cellular lineages. This hypothesis of a potential HIV infection of HPCs may further imply an important feature in the dynamics of HIV disease: long-lived HPCs may harbour proviral HIV DNA genomes in their own genomes and act as an additional reservoir of HIV. Interestingly, cellular HIV receptors and co-receptors can be detected on HPC cell membrane. Flow cytometry analyses showed that 25%-65% of CD34+ HPCs that had been purified from the BM of healthy donors, expressed detectable levels of CD4 protein on their cell membranes[18,19]. Moreover, the CD4 protein was functionally active, and it effectively bound the HIV-1 gp120 anti-receptor[19]. The major co-receptors CXCR4 and CCR5 were also expressed on HPC cell membranes[20-22], and CXCR4 and CCR5 proteins were expressed in 53% and 35% of isolated CD34+ HPCs, respectively[23]. However, the analysis of CXCR4 and CCR5 expression was dependent on the differentiation stage. When the expression levels of CXCR4 and CCR5 were determined in CD34+/CD38- and CD34+/CD38+ HPC subsets, the CXCR4 protein expression level was relatively constant in both subsets whereas CCR5 was detected in 2% of more primitive CD34+/CD38- cells and in 35% of more mature CD34+/CD38+ subset, which indicated that CCR5 but not CXCR4 is up-regulated during differentiation from HSC into MPP[23]. The expression of HIV receptors and co-receptors on the cell membranes of CD34+ HPCs suggested that these cells could be considered a possible target of HIV infection.

To explore this hypothesis, two major experimental approaches were undertaken by several groups: (1) the challenge of BM or cord blood CD34+ HPCs, isolated

from uninfected donors, with HIV strains; and (2) the detection of HIV nucleic acids and/or viral proteins in BM CD34+ HPCs isolated from HIV-positive patients. These studies were based on the isolation and purification of CD34+ HPCs that represent a heterogeneous cell population[24,25] because the CD34+ marker could be detected not only on HSCs and MPPs but also on more committed myeloid progenitors such as CFU-GEMM, CFU-GM, BFU-E and CFU-MK progenitors.

Several reports showed that CD34+ BM HPCs, purified from uninfected donors, were resistant to HIV infection. Polymerase chain reaction (PCR) or reverse transcriptase-PCR analysis of proviral HIV DNA or HIV RNA in HPCs that had been challenged with different HIV-1 strains did not reveal significant evidence of HIV infection[9,12,26-29]. In partial contrast to these data, Chelucci and coworkers[30] have purified CD34+ HPCs from the peripheral blood of healthy donors, cultured them with EPO + granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3) and SCF and then challenged with different HIV-1 strains. The analysis of p24 protein showed that 12% of CFU-GM and less than 1% of BFU-E colonies were positive whereas the CFU-GEMM progeny were negative.

Interestingly, early stem cells in the CD34+ HPCs, which are arrested in the G_0 phase of the cell cycle, were not permissive for HIV infection[23], and other reports showed that the more primitive CD34+/CD38- HPC subset was not susceptible for HIV-1 or HIV-2 infection[31,32]. However, a limited infection was revealed in the first weeks of long-term culture in CD34+/CD38+ HPCs, which suggested that HIV infects at low extent only the more committed HPC subset but not the more primitive HPCs[31].

The analysis of HIV infection in BM HPCs, purified from HIV-positive patients, was carried out to determine whether these patients could harbour proviral HIV DNA in HPCs. Two studies[33,34], based on PCR assays to detect proviral HIV DNA in BM HPCs, reported that 1 out of 14 patients and 1 out of 11 patients, respectively, were HIV DNA positive. Similar percentages of HIV proviral DNA positive samples were detected in subsequent reports[12,13,35]. In contrast with these results, a higher percentage of HIV-1 infection of CD34+ HPCs was observed in some groups of HIV-1 positive individuals especially in patients with the more advanced stages of the disease[36,37]. This discrepancy could be related to the use of different PCR assays with different sensitivities, and the possible presence of contaminating HIV-infected BM stromal cells.

Notwithstanding these controversial results, the consensus on HPC susceptibility to HIV infection, was that *in vitro* infection of HPCs occurred, under some experimental conditions, in a low fraction of HPCs, and these HPCs were the more committed HPCs, whereas the more primitive HPCs were not considered a significant HIV target. Moreover, *in vivo* infection of HPCs was infrequent suggesting a negligible role of HIV-infection of HPCs in BM derangement and the induction of cytopenias[7].

Several mechanisms have been proposed to explain HPC resistance to HIV infection. HPCs secrete the CCR5 ligands macrophage inflammatory protein-1α (MIP-1α), MIP-1β, and regulated on activation normal T cell expressed and secreted (RANTES)[37,38] and the CXCR4 ligand stromal-derived factor 1 (SDF-1)[22], which may compete with R5- or X4-tropic HIV-1 strain infection by interfering with gp120/co-receptor-binding. In addition, an analysis of the interference between gp120 and mAb directed against CXCR4 in HPCs, suggested the lack of a real CD4/CXCR4 complex on HPC membranes, which excluded the formation of the trimeric complex with gp120, essential for HIV binding and infection[22]. Zhang and coworkers have also showed that the cellular cyclin-dependent kinase inhibitor p21 protein restricts HPC infection and interferes with the integration of the proviral HIV-1 genome[39].

However, recent studies have challenged the consensus about HPC resistance to HIV infection[40-44]. A report has described the HIV-1 subtype C infection in CD34+ HPCs, and the analysis of proviral HIV DNA in peripheral blood CD34+ cells showed that 12 out of 19 patients were positive. Interestingly, HIV-1 subtype B strains were not able to infect HPCs, suggesting that only specific HIV subtypes could be associated with direct infection of HPCs[40]. Carter *et al*[41] challenged purified HPCs with a molecular HIV clone p89.6 derived from the dual tropic HIV strain 89.6. A small percentage (1%-6%) of HPCs exhibited HIV-1 gag protein expression 72 h post infection. A similar infection rate was found, in contrast with previous studies, even in the more primitive CD133+CD34+CD38- HPC subset. However, the methodological approach of this study was subsequently criticised for the choice of the sole criterion of gag analysis, the infection protocol and the pseudo-viruses that were used[45]. These results were substantially confirmed by the same group in a subsequent study[42] that showed HIV infection in approximately 2% of primitive CD133+CD34+^{high} HPC subset cells. HIV infection was detectable when X4-tropic HIV subtype B strains were used, whereas R5-tropic HIV strains were ineffective on CD133+CD34+CD38- HPC subset cells, suggesting that the infection of HPCs might be detectable when X4-tropic HIV strains appear during the progression of HIV infection. These X4-tropic HIV strains are generally observed in the late stages of HIV infection and are related to more rapid disease progression and a poorer prognosis.

Carter *et al*[41] have also studied BM HPCs, isolated from six HIV-positive patients with high HIV RNA load. HIV-1 gag protein was detected in three of the six samples. When these cells were cultured with GM-CSF and tumour necrosis factor-α (TNF-α) to induce myeloid differentiation, all six of the samples were positive for the gag protein. In the same report, fresh BM HPCs, isolated from nine combination antiretroviral therapy (cART)-treated HIV positive individuals with undetectable viral loads for longer than 6 mo, were analysed using a quan-

titative real time PCR assay for integrated proviral HIV DNA. Four of the nine samples were positive with the number of proviral HIV genomes ranging between 2.5-40 copies/10000 CD34+ HPCs. These data suggested a new interpretation of the interaction between HIV and HPCs, in which a low number of HSCs and HPCs are susceptible to HIV infection and may represent an HIV reservoir. The rate of infection could be under-recorded because the data from Carter *et al*[41] indicate that HIV challenge is cytotoxic for HPCs. Moreover, their studies showed that even HIV-1 subtype B strains could infect these HPC subsets, which is in contrast to the previous study indicated above[40], suggesting that the HIV-1 subtype B cytotoxicity could explain this phenomenon. The infection of HPCs indicated that these cells could be a reservoir of HIV. Unfortunately, the hypothesis of HPCs as a viral reservoir was not confirmed by two subsequent analyses on proviral HIV-1 DNA in HPCs[46,47]. In these studies, CD34+ HPCs were purified from 11 and 8 HIV-positive patients treated with long-term suppressive cART. High sensitivity PCR assays demonstrated no HIV-1 proviral DNA in these cells[46,47].

Altogether, these recent studies have reconsidered the relationship between HIV infection and HPCs, but the data still remain controversial and further studies are needed to evaluate whether HIV infection of HPCs may be associated with the onset of blood cytopenias or may represent an additional HIV infection reservoir.

In addition to analyses of the direct infection of HPCs by HIV, several studies have been performed on granulocyte-macrophage CFUs (CFU-GMs), mixed lineage CFUs (CFU-GEMMs) or erythroid burst-forming units (BFU-Es). In this context, HPCs from HIV-1 infected patients, showed impaired *in vitro* BFU-E, CFU-GM and BFU-MK growth[12,25,27,34,36,48,49]. These results were confirmed even in HPCs purified from HIV-negative individuals and challenged with HIV even though other studies did not observe growth inhibition[26,30,50,51] probably due to the different HIV strains and cell culture conditions that were used. The significant reduction of CFU-GEMM, CFU-GM, BFU-E, and BFU-MK growth suggested an alteration of HPC proliferation with the possible involvement of apoptosis in the induction of cytopenias. Apoptosis plays an important role in the depletion of CD4+ T lymphocytes even through the interaction of HIV gp120 and CD4. HIV gp120 is also able to induce the activation of apoptosis in endothelial cells, osteoblasts, and neurons[52-54], and several studies have been performed on the effects of heat-inactivated HIV and certain viral proteins such as gp120 and Tat on the myelosuppression observed in HIV-positive patients. HIV-1 gp120 and heat-inactivated HIV-1[28,31,55,56] impaired the *in vitro* clonogenic capacity and induced apoptosis. This negative regulation of proliferation and survival was associated with transforming growth factor β1 (TGFβ1) increased production by HPCs and the occurrence of a Fas-dependent mechanism[57,58]. This reduction in survival and proliferation due to apoptosis could at least partially explain the decrease of HPCs and circulating precursors that has been noted in HIV-positive patients[13,34,36,56-62].

HIV AND BM STROMAL CELLS

The cellular components of the BM include HPCs at all stages of differentiation and stromal cells. BM stromal cells are a mixed population composed of mesenchymal stem cells (MSCs), endothelial cells, macrophages, fibroblasts, adipocytes, osteoblasts and osteoclasts, as well as dendritic cells and B and T lymphocytes that migrate from the blood to the BM. Stromal cells are essential for proper homeostasis and the regulation of BM haematopoiesis through a complex cellular cross-talk that is modulated by cytokines. *In vitro* experiments using long-term BM cultures showed that HIV-infected BM stroma was unable to support uninfected CD34+ HPC growth and differentiation compared to uninfected cultures[49,63,64]. In addition, the stromal structure of the BM in HIV patients shows morphological variations including an increased number of macrophages and a decreased number of fibroblasts[10,65]. This impairment of stromal activity and structure affects HPC differentiation and growth and it is due to the complex interaction between HIV and the different BM stromal cells that lead to a derangement of cytokine regulation. In particular, certain cell types, such as T cells, MSCs, macrophages and endothelial cells, are targeted, directly and indirectly, by HIV and its proteins including Tat and gp120[66-69]. BM MSCs can differentiate towards several cell lineages such as osteoblasts, adipocytes, fibroblasts, *etc*. *In vitro* experiments have demonstrated that HIV, gp120 and Tat can elicit a derangement of the clonogenic capacity of BM MSCs. In particular, the osteoblast differentiation is inhibited whereas adipocyte differentiation is increased. The alteration of the clonogenic activity may also explain the decreased number of fibroblasts that are detectable in the BM of HIV patients[10,65]. T cells, macrophages, endothelial cells and MKs are productively infected by HIV to different degrees in the BM. Endothelial cells are permissive for HIV infection and BM endothelial cells are infected in HIV patients at every stage of HIV disease. Endothelial cell infection was related to BM impairment in HIV-positive subjects because they exhibited a reduced ability to respond to BM micro-environmental regulatory signals that positively up-regulated the number of blood cells[69].

CD4+ T cells and macrophages are the major targets of HIV replication, and the release of specific cytokines and haematopoietic factors is affected by HIV infection. TNFα, TGFβ1, interferon-γ (IFN-γ), IL-1, IL-6, IL-10, IL-18, TNF-related apoptosis-inducing ligand and monocyte colony-stimulating factor are dysregulated by HIV in T cells and monocyte models[70-75]. Similarly, viral proteins such as Tat and/or gp120 increase the expression of IL-6, TNFα and IL-1[76-81]. The impairment of several cytokines during HIV infection was confirmed by clinical studies in which higher levels of IL-1, IL-18, TNFα and IL-6 in the plasma of HIV-positive patients were

detected compared to uninfected individuals[82-85]. It is noteworthy that the pro-inflammatory cytokines TNFα, IL-1, and IL-6 and the chemokines MIP-1α, MIP-1β and RANTES were up-regulated in the BM of HIV-positive patients[65,86]. TNFα involvement in the HIV-1-induced suppression of haematopoiesis, was also suggested in neutralisation studies[87]. Tat is able to elicit a significant activation of the TGFβ1 expression in macrophages that have been isolated from BM. BM macrophage culture supernatants were added to BM HPC cultures thus inducing an inhibition of HPC growth in the liquid cultures[88]. This chronic derangement of cytokine modulation can elicit several negative effects on HPCs and their differentiation into various cell lineages, cooperating in the pathogenesis of anaemia and thrombocytopenia in HIV-infected patients.

HIV AND THE MK LINEAGE

Chronic thrombocytopenia is detectable during HIV disease in approximately 10% of HIV positive patients and 15%-60% of patients with AIDS[89-92]. This haematological disorder may represent the first manifestation of HIV infection and it may progress over time and lead to severe bleeding[91]. HIV-associated thrombocytopenia is related to reduced platelet survival, ineffective platelet production and the impairment of the survival of BM MKs and their precursors. HIV targets the MK cell lineage by interfering throughout the differentiation of mature MKs (Figure 2A). As described above, HIV decreases the number and activity of HPCs and induces a growth deficit in CFU-MKs in HIV patients. An analysis of the impact of HIV-1 and gp120 during TPO-induced cord blood-derived HPC differentiation into MKs has demonstrated that gp120 treatment led to the induction of apoptosis in the CD41+ and CD61+ subsets due to TGFβ1 increase and APRIL down-regulation[55]. These data confirmed the induction of apoptosis through the gp120 engagement of CD4, observed in BM GP Ⅱb/Ⅱa+ (CD41+) megakaryocytic cells and in megakaryocytic cell line models[93-95]. Moreover, a reduction of c-mpl expression in the MK lineage due to V3 loop region of gp120 was observed in MK lineage thus indicating a further mechanism involved in the impairment of megakaryocytopoiesis[96].

HIV and gp120 altered the maturation of MKs, and decreased the number of MKs with higher ploidy[55]. Electron microscopy analysis of MKs from HIV-infected individuals with thrombocytopenia clearly demonstrated ultrastructural abnormalities, such as blebbing of the surface membrane and vacuolisation of the peripheral cytoplasm[97]. Mature MKs can be infected by HIV through binding the CD4 receptor[97-102], and HIV genomes have been detected in MKs purified from BM of HIV-positive patients[103]. The infection of MKs is not strain-restricted because both R5- and X4-tropic HIV-1 strains are able to infect MKs thus indicating that the infection may occur early in the development of HIV infection[99]. In addition to these direct effects of HIV on the MK cell lineage,

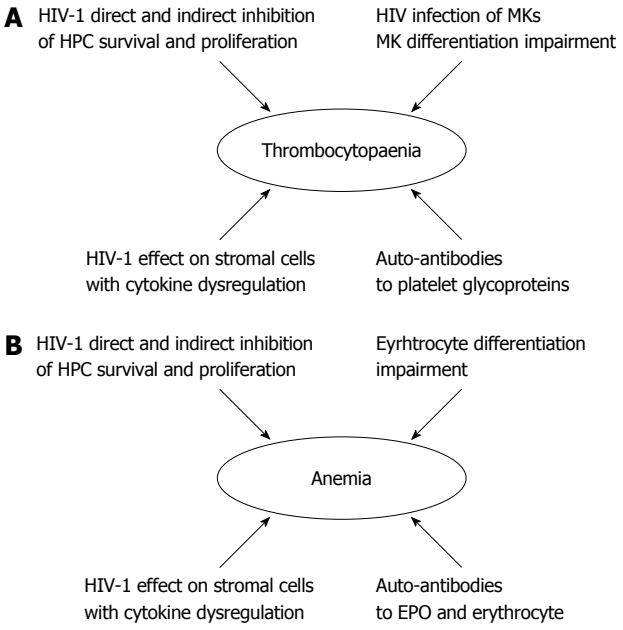

Figure 2 The mechanisms involved in human immunodeficiency virus-related thrombocytopenia and anaemia. A: Human immunodeficiency virus (HIV)-related thrombocytopenia; B: HIV-related anaemia. EPO: Erythropoietin; HPC: Haematopoietic progenitor cell; MK: Megakaryocyte.

HIV also supports chronic thrombocytopenia through autoimmune mechanisms[89-92], particularly evident in early stages of the disease[104,105]. Autoimmune mechanisms are related to anti-HIV antibodies cross-reacting with platelet-membrane glycoproteins, supporting the basic role of molecular mimicry in the induction of these antibodies[106-110]. In particular, an autoantibody directed against integrin GP Ⅲa49-66 induced a platelet lysis[110] and cross-reacted with some peptides derived from Nef and gp120[111]. The anti-GPⅢa49-66 antibody isolated from HIV-1 patients down-regulated MK proliferation in *in vitro* culture of human cord blood CD34+ cells driven by TPO[112].

Platelets can bind HIV-1 gp120 through its CXCR4 and fibronectin surface receptors, and platelet-bound HIV may infect permissive cells suggesting a possible role for platelets as carriers in the spread of HIV infection[113]. The interaction between platelets and HIV leads to the activation of platelets and an altered platelet morphology, which is likely due to CXCR4 binding because this protein is the receptor of SDF-1, a factor involved in enhancing platelet activation by agonists[114]. Platelet activation was detected in HIV patients and the degree of activation in circulating platelets was higher in AIDS patients than patients in earlier stages of HIV infection[115]. Activated platelets also represent a source of some pro-inflammatory cytokines. Their activation led to a strong induction of IL-1β and IL-18 secretion eliciting a further cytokine regulation derangement[114,116]. These alterations of platelet activity were also related to the impairment of coagulation homeostasis, thus increasing the complexity of the HIV/MK/platelet/coagulation interactions. These studies demonstrated that the MK lineage is a direct and

indirect target of HIV and its proteins throughout their entire differentiation and development. This targeting affects platelet maturation and activity, explaining why thrombocytopenia is a major cytopenia in HIV-positive patients.

HIV AND THE ERYTHROCYTE CELL LINEAGE

Anaemia is a clinical complication detectable in many HIV patients[117]. The overall incidence of anaemia in HIV-positive individuals is 10% in asymptomatic patients and up to 92% in patients with AIDS[6,117]. cART treatment has reduced but not solved the problem of anaemia in HIV patients. In a cohort of 1624 patients in the EuroSIDA study, the prevalence of anaemia during HAART decreased from 65% in naive patients to 53% after 6 mo of therapy and 45% after 1 year of therapy[118]. Although anaemia does not generally cause death in HIV patients, it is well known that anaemia can increase morbidity in these subjects. HIV patients with anaemia have a higher risk of reduced survival compared to non-anaemic in HIV positive patients[117,119]. The symptoms of anaemia during HIV infection are not different from the symptoms that are observed in HIV negative patients, and the diagnosis of anaemia is often a laboratory diagnosis based on a reduction of the haemoglobin (Hb) value and erythrocyte count. The anaemia is generally mild with Hb concentrations between 8-14 g/dL for men and 8-12 g/dL for women, although the degree of anaemia is dependent on the immunosuppressive context and disease stage[120]. The erythrocyte morphology does not exhibit consistent variations in the peripheral blood[121]. Microcytosis is rarely observed, whereas macrocytosis is found in HIV-positive patients treated with zidovudine (AZT). AZT treatment was related to BM suppression, and the HER and WIHS studies observed a significant increase in anaemia in AZT-treated patients[122,123]. Some reports indicated the presence of poikilocytosis, anisocytosis and ruleaux formation, but, in general, HIV-associated anaemia is characterised by normocytosis, low reticulocyte counts and an ineffective erythropoiesis with an hyporegenerative BM[6,124]. The pathogenesis of anaemia in HIV-positive patients is multifactorial (Figure 2B): the different mechanisms that are involved in the anaemia induction are characterised by the impairment of erythrocyte production and increased erythrocyte destruction[120]. HIV is directly involved in the induction of anaemia even though neoplastic diseases, vitamin deficiencies, iron metabolism impairment, pharmacological treatments and opportunistic infections are implicated in anaemia onset during HIV infection. The involvement of HPCs in the cytopenias has been illustrated above, however, it is noteworthy that Cleveland and coworkers observed the expression of CD4 on the cell membranes of erythroid differentiating cells. The co-expression of CD4 and glycophorin A indicates that some erythroid-committed cells could represent a target for HIV infection[125]. In addition, the expression of functional CXCR4[37] was detected in CD34+ BFU-Es even though its expression level decreased during erythroid differentiation. Interestingly, Tat treatment of cord blood-isolated HPCs up-regulated CXCR4 protein expression indicating a complex effect of HIV activity on erythrocyte lineage survival and differentiation[126]. Moreover, the dysfunction of erythroid differentiation could be related to BM microenvironment damage and stromal cell impairment[7,71]. IL-1β, IFN-γ, TGFβ1 and TNFα suppress the growth of progenitor cells *in vitro* and may play an important role in the induction of HIV-associated anaemia[116,126,127]. Some papers have suggested that HIV could impair the EPO-related feedback mechanisms that regulate the red blood cell homeostasis. Decreasing the Hb concentration induces EPO production, whereas in many HIV patients the presence of anaemia is coupled with a decrease in the serum EPO concentration that is independent of kidney damage[121,128,129]. Moreover, *in vitro* experiments demonstrated that HIV-1 reduced EPO synthesis[130]. Different mechanisms have been considered to explain this EPO reduction. HIV-related up-regulation of pro-inflammatory cytokines IL-1β and TNF-α directly down-regulates EPO expression *in vitro*[131] through the cytokine-mediated formation of reactive oxygen species, which in turn impair the binding affinities of EPO-inducing transcription factors. In addition, circulating antibodies to EPO are detectable in approximatively 23% of HIV-infected patients, and a prospective study on 113 patients showed that anti-EPO antibodies could be considered an independent risk factor for anaemia[132,133]. The presence of these auto-antibodies, directed against several targets, was associated with molecular mimicry and the dysregulation of the immune system. Recent reports demonstrated that the anti-EPO antibodies recognised three major EPO molecule epitopes that span three regions including the amino acids domains 1-20 (EP1), 54-72 (EP5) and 147-166 (EP12) of which EP1 and EP12 are the domains that are involved in the EPO-EPOR interaction[134]. The region corresponding to EP1 shows a 63% sequence homology with the 34-52 amino acid sequence of HIV gag p17, and a cross-reaction between anti-EP-1 auto-antibodies and the gag fragment was detected suggesting a role for mimicry by this protein in the occurrence of anaemia[134]. HIV-associated anaemia could also be induced by haemolysis. In HIV patients, cases of haemolysis have been observed that are linked to CID, glucose-6-dehydrogenase deficiency, auto-antibodies against red blood cells, thrombotic thrombocytopenia purpura and pharmacological treatment. Furthermore, some HIV positive patients exhibited the presence of a broad panel of specific and non-specific anti-erythrocyte antibodies, and, in some cases, erythrocyte lysis was mediated by complement activation. Although consistent haemolysis is rare in HIV patients, the damage and lysis of red blood cells by auto-antibodies can be considered an additional mechanism of HIV-associated anaemia[135-137].

In conclusion, the occurrence of thrombocytopenia and anaemia represent major pathological manifestations

in HIV patients. The pathogenesis of these cytopenias is multifactorial, and several targets such as HPCs, cell lineage differentiation, cytokine dysregulation and stromal cell impairment cooperate in the occurrence of these haematopoietic defects. The investigation of the different mechanisms that are involved in the genesis of these cytopenias has provided important findings on HIV pathogenesis even though some pivotal items such as the susceptibility of HPCs to HIV infection and their role as HIV infection reservoirs are still under debate and deserve additional experimental analysis. Further studies will be essential to better characterise these mechanisms and to identify useful targets for supportive therapy and management of HIV-positive patients.

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