ROLE OF HIV-1 IN THE FUNCTIONAL IMPAIRMENT OF CD34⁺ HEMATOPOIETIC PROGENITOR CELLS

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ABSTRACT

The role played by HIV-1 infection in the pathogenesis of peripheral blood cytopenias frequently found in HIV-1 seropositive individuals was initially elusive. However, a body of in vivo and in vitro experimental evidence suggests that HIV-1 can be directly involved in the suppression of hematopoietic progenitor cells through either direct or indirect mechanisms: (1) infection (productive or non-productive) of a subset of CD34⁺ hematopoietic progenitor cells, co-expressing the CD4 antigen with growth defects of infected cells; (2) membrane interactions of CD34⁺ hematopoietic progenitor cells with HIV-1 virions or immune complexes containing env gp120, which can directly lead CD34⁺ cells to apoptotic cell death. Both the viral load and the biological characteristics of the virus play an important role in causing these suppressive effects, since different isolates displayed a differential ability to suppress hematopoiesis; (3) infection with HIV-1 and/or exposure of bone marrow accessory cells to viral proteins (gp120 and Tat) with increased production of inhibitory factors, such as TNF-α or TGF-β1.

Hematologic disorders are frequently observed in the majority (70-80%) of HIV-1 infected patients during the course of HIV-1 disease (1-2). Most peripheral blood cytopenias take place in symptomatic patients and usually their frequency increases as the disease progresses towards overt acquired immunodeficiency syndrome (AIDS). On the other hand, isolated thrombocytopenia can occur early in the natural history of HIV-1 infection as an isolated hematological manifestation (3).

It is fairly well established that the pathogenesis of hematological abnormalities in AIDS patients is multi-factorial (1-2). In particular, B cell lymphomas spread to the bone marrow, a variety of opportunistic agents and a reduced production of erythropoietin can

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significantly contribute to the bone marrow suppression. Moreover, peripheral blood cytopenias in HIV-1 infected individuals can be markedly worsened by the treatment with zidovudine (4-5) or other anti-retroviral or antineoplastic agents. The main clinical relevance of peripheral blood cytopenias in HIV-1 infected patients is represented by the fact that they often entail the discontinuation or suspension of zidovudine or cytotoxic therapy.

A body of experimental evidence, however, suggests that also HIV-1 infection may be directly involved in the pathogenesis of peripheral blood cytopenias of HIV-1 seropositive individuals through different mechanisms: (i) infection of mature hematopoietic precursors; (ii) infection of marrow accessory cells; (iii) inhibitory interaction(s) of HIV-1 virions with CD34+ cells.

The paradigmatic example of HIV-1 infection of mature hematopoietic cells is represented by infection of bone marrow megakaryocytes, which occurs in at least 50% of HIV-1 seropositive individuals harbouring a peripheral thrombocytopenia (6-7) and it is thought to result in a reduced production of platelets.

A productive infection of cells belonging to the bone marrow microenvironment of HIV-1 seropositive subjects (8-12), in particular of T lymphocytes (8-9) and monocytes (10), has been demonstrated. Such infection might induce disruption of the physiological control of hematopoietic stem/progenitor cells by an imbalanced cytokine production (13-14). Moreover, the experimental infection of long term bone marrow cultures (LTBMCs) pointed out that the viral burden and the kind of viral isolate used to infect LTBMCs may be critical factors in the HIV-1 mediated suppression of hematopoiesis (15-17).

Several defects in the colony forming ability of hematopoietic progenitors have been identified in HIV-1 infected individuals (20-29). The general picture emerging from all these studies is that the frequency of hematopoietic progenitor cells in the marrow and peripheral blood of HIV-1 infected individuals progressively decreases as the disease progresses. The only remarkable exception is represented by patients with isolated and persistent thrombocytopenia, who showed a selective defect of the CFU-Meg progenitor cell compartment (28).

At least two distinct mechanisms of inhibition are responsible for the impaired colony growth of hematopoietic progenitor cells in HIV-1 seropositive patients (Table 1): an indirect suppression by accessory cells present in the bone marrow and peripheral blood samples and an intrinsic defect in stem/progenitors. Evidence for an inhibitory activity of accessory cells comes from studies showing that the defective colony formation could be partially restored by either T-cell depletion (18,24), treatment of marrow cells with anti-sense oligonucleotides to Tat or nef regulatory gene sequences (13) or addition of anti-TNF-α in culture (26). However, also purified CD34+ cells from symptomatic HIV-1 seropositive individuals are defective in colony formation (8, 25, 27-29), which implicates the presence of an intrinsic defect of the stem/progenitor cells.

Several groups of investigators have attempted to evaluate whether the reduced colony forming ability of hematopoietic progenitors cells in HIV-1 seropositive individuals could be due to a direct HIV-1 infection of CD34+ cells. As summarized in Table 2, most investigators reported rare infection of CD34+ cells, purified from the bone marrow of HIV-1 seropositive individuals at various stages of the disease (8-9, 15, 25, 28-30). The higher percentage of low level (1 proviral DNA copy in 500 CD34+ cells) infection was reported by Stanley et al. (27) in a significant subset of HIV-1 seropositive patients with advanced stage disease. Also the presence of proviral DNA in hematopoietic colonies at the end of the culture time was only occasionally reported (15, 27). Consistently, a number of studies have reported the ability of HIV-1 to infect in vitro CD34+ cells purified from either normal bone marrow (31-33) or peripheral blood (34) and the presence of proviral DNA has been recovered in fully developed granulocyte/macrophage and erythroid colonies. The picture emerging from all these studies clearly suggests that infection of CD34+ hematopoietic