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Loss of Hematopoietic Progenitor Cells CFU-GEMM, BFU-E, CFU-Mk, and CFU-GM in the Acquired Immunodeficiency Syndrome (AIDS)? *

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A. Introduction

Hematological abnormalities have been found in the majority of patients with AIDS, in addition to immunological derangements [1]. Furthermore, treatment of opportunistic infections with folic acid antagonists and of neoplasms with cytostatic drugs is frequently complicated by profound thrombocytopenia, neutropenia, and anemia, thus resulting in the withdrawal of the drugs.

In the present study we therefore analyzed the hematopoietic progenitor cell compartments, using an in vitro culture system that allows colony formation by the pluripotent progenitor cells CFU-GEMM and by the unipotent erythroid progenitors BFU-E, the megakaryocytic progenitors CFU-Mk, and the granulocytic-monocytic progenitors CFU-GM [2].

B. Materials and Methods

Bone marrow cells from patients with AIDS and from normal controls were obtained from the posterior iliac crest after informed consent. Light-density cells (<1.077 g/ml) or cells that had been depleted of T cells by a rosetting technique with AET-treated sheep red blood cells [3] were cultured at 10^5 cells/ml in Iscove's modified Dulbecco's medium supplemented with 30% fresh frozen human plasma, 5%–10% PHA-leukocyte – conditioned medium, 50 μM 2-mercaptoethanol, and 1 U/ml erythropoietin (Connaught, Step III). After 14 days at 37 °C and 5% CO_2 in air, colonies were counted using an inverted microscope [4].

C. Results and Discussion

A total of nine patients with AIDS ($n=7$) or advanced lymphadenopathy syndrome ($n=2$) were analyzed. All of the patients with AIDS had Kaposi's sarcoma. T4-lymphocytes in the blood were reduced to 149/mm^3 (range 11–681; normal 1100–1300) and T8-lymphocytes increased to 533/mm^3 (range 107–1308; normal 350–450). At the time of bone marrow aspiration, anemia was observed in six of the patients, thrombocytopenia in two, and neutropenia in one.

In all patients, the in vitro colony formation was reduced for all four types of progenitor cells (Table 1). To find out whether the reduction in colony formation was due to an actual deficiency of progenitor cells or due to their impaired in vitro proliferation resulting from altered "accessory" T-cell subsets [5], T-cells were depleted from the bone marrow cells prior to culture. In contrast to normal controls, T-cell depletion from AIDS-derived bone marrow cells was followed by a significant increase in colony formation of all four types of progenitors; however, normal values were obtained only in three out of nine patients. Colony formation significantly increased from 1.0 ± 0.3 to 3.4 ± 1.3 (mean $\pm$ standard error of mean)

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Table 1. Growth of hematopoietic progenitors in AIDS (colonies per 10^5 cells ± SEM)

	CFU-GEMM	CFU-Mk	BFU-E	CFU-GM
AIDS ($n=9$)	1.0±0.3	1.4±0.7	5.3± 2.5	18± 5
Normal ($n=24$)	15 ±4	15 ±2	117 ±42	84±16
P value	<0.01	<0.05	<0.001	<0.001

per 10^5 cells for CFU-GEMM; from 5.3±2.5 to 19.9±8.7 for BFU-E; from 1.4±0.7 to 5.6±2.2 for CFU-Mk; and from 17.9±5.2 to 42.8±13.2 for CFU-GM.

Readdition of the previously isolated T cells to the autologous T-cell-depleted marrow cells at a 1:1 ratio again resulted in a significant decrease in colony formation which was not observed in the normal controls. Since the percentage of inhibition was inversely correlated to the T4:T8 ratio, the reduced in vitro growth of the hematopoietic progenitor cells can partially be explained by growth inhibition due to the T4:T8 imbalance.

To exclude impairment of in vitro colony growth of AIDS-derived progenitor cells by soluble factors, cocultures of AIDS-derived bone marrow cells with irradiated or nonirradiated normal bone marrow cells were carried out. However, no change in the in vitro growth of normal or AIDS-derived progenitor cells was observed in either case. While inhibition by soluble factors, e.g., interferons, is unlikely, inhibition by cell-cell interaction could still account for the effects observed, because these interactions might depend on autologous coculture conditions [6].

However the inability in the majority of our cases to completely restore colony formation by T-cell depletion might indicate that in more advanced infections with HTLV-III/LAV the number of pluripotent and unipotent hematopoietic progenitor cells is reduced owing to a still unknown mechanism which might include infection of stem cells by HTLV-III/LAV, leading to failure of the hematopoietic system in situations of stress.

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