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Killer Cells in Leukemia *

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A. Introduction

Killer cells can be analyzed in the context of human leukemia in three different ways:

1. The cytotoxic potential of nonleukemic cells found in a leukemic sample can be analyzed.
2. The leukemic cells can serve as targets for cytotoxic cells.
3. Leukemias can represent transformants of killer cells. In the following we will summarize in brief our results on these separate topics.

B. Materials and Methods

Leukemic cells from peripheral blood, classified by morphology, cytochemistry, and immunologic markers, were used either fresh or after storage in liquid nitrogen. Analysis with monoclonal antibodies (MoAb) was done in indirect immunofluorescence and cytotoxicity was studied by chromium release.

C. Results and Discussion

In chronic lymphocytic leukemia (CLL), the deficiency of the immune system appears to be of utmost importance for the outcome of the disease, since infections and secondary malignancies are major causes of death. When the nonleukemic cells were isolated from peripheral blood samples of CLL patients, the natural killer (NK) cell activity was found to be profoundly defective in a large portion of patients [1]. At the cellular level, this might be explained: (a) by the presence of functionally defective mature effector cells; or (b) by the absence of the effector cells. Using the MoAb HNK-1 [2] which detects mostly early inactive NK cells plus some active NK cells, and the MoAb VEP13 [3] which detects active NK effector cells only, we found that in patients with defective NK cell activity the VEP13$^+$ cells were absent while the HNK-1$^+$ cells were increased [4] (Fig. 1a). We suggest that there might be a block in differentiation of the NK cells in CLL, which results in accumulation of precursor cells.

In analyzing acute leukemia cells as target cells, we were able to demonstrate that the cell-mediated killing of these cells can be greatly enhanced by a short preincubation with actinomycin D [5]. The allogeneic effector cells responsible for this lysis could either be T cells, monocytes, or NK cells. Using the MoAb VEP13, we were able to demonstrate the NK cell nature of the effector cells [6] (Fig. 1b). The results point to a possible cooperation of cytostatic drug and the immune system and further studies will have to test this possibility in autologous combinations.

We have developed a system that allows for measurement exclusively of cytotoxic monocytes against tumor cells in a short-term (7 h) assay with whole peripheral blood mononuclear cells [7]. For the analysis of clonal killer monocytes, we used cells

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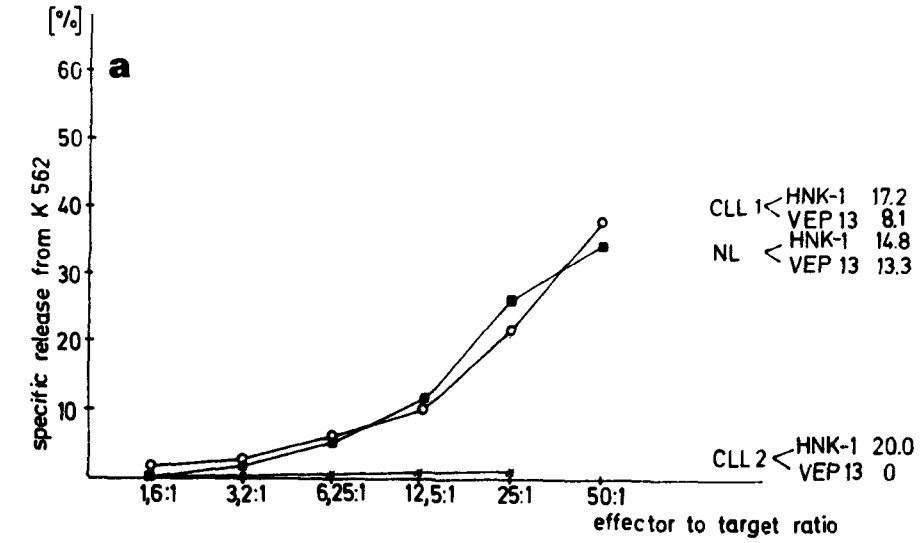

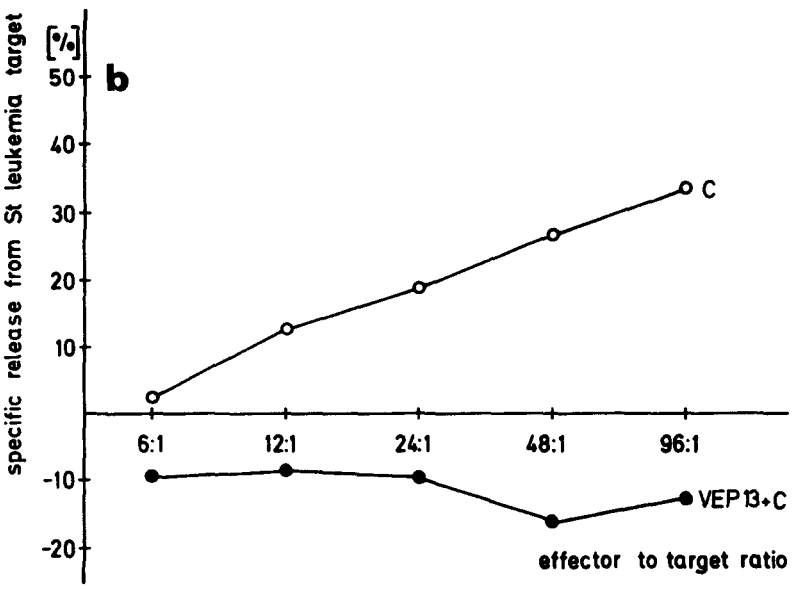

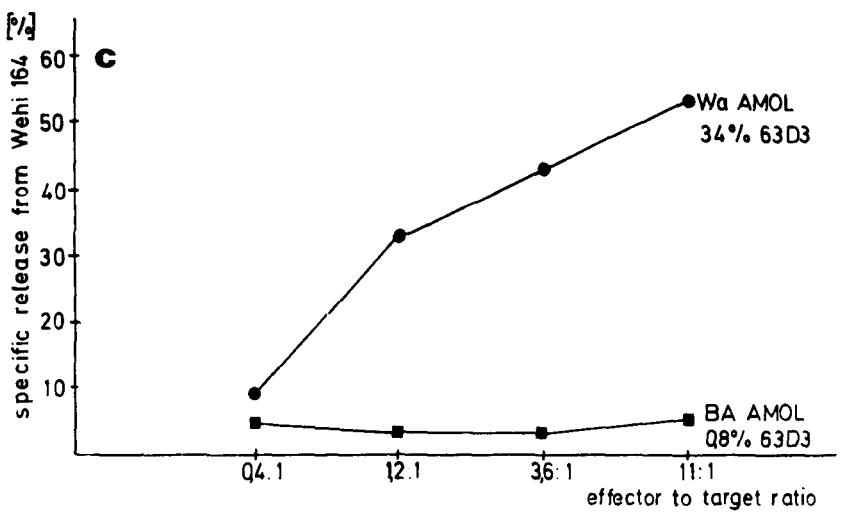

Fig. 1 a–c. **a** NK cell activity of nonleukemic cells obtained after BA-1 plus complement treatment from two CLL patients and one control; **b** Phenotype of spontaneous killer cells active in enhanced killing of allogeneic leukemia cells. Interferon-treated effector cells lyse actinomycin D-treated leukemia cells. Killing is abrogated by treatment with VEP13 plus complement; **c** Cytotoxicity of monoblastic leukemia cells against a monocyte-specific fibrosarcoma cell

from acute monoblastic leukemia (AMoL) patients and we found that AMoL cells can exert high cytotoxicity which is linked to the expression of a MoAb-defined cell surface marker (63D3) [8, 9] (Fig. 1c). In conclusion, analysis of killer cells in leukemia can increase our understanding of the normal regulation of these important effector cells of the immune system and at the same time it can provide information useful for the management of the disease and for designing new therapeutic strategies.

References

1. Ziegler HWL, Kay NE, Zarling JM (1981) Deficiency of natural killer cell activity in patients with chronic lymphocytic leukemia. Int J Cancer 27:321
2. Abo T, Miller CA, Balch CM (1984) Characterization of human granular lymphocyte subpopulations expressing HNK-1 (Leu 7) and Leu 11 antigens in the blood and lymphoid tissues from fetuses, neonates and adults. Eur J Immunol 14:616
3. Rumpold H, Kraft D, Obexer G, Böck G, Gebhard W (1982) A monoclonal antibody against a surface antigen shared by human large granular lymphocytes and granulocytes. J Immunol 127:1024
4. Ziegler-Heitbrock HWL, Rumpold H, Kraft D, Wagenpfeil C, Munker R, Abo T, Balch CM, LeBien TW (1985) Patients with a deficiency of natural killer cell activity lack the VEP13 positive lymphocyte subpopulation. Blood 65:65
5. Ziegler-Heitbrock HWL, Erhardt J, Riethmüller G (1983) Treatment of fresh human leukaemia cells with actinomycin D enhances their lysability by natural killer cells. Br J Cancer 48:507
6. Ziegler-Heitbrock HWL, Fütterer A, Rumpold H, Kraft D, Munker R, Riethmüller G (1984) The use of VEP13 monoclonal antibody for definition of natural killer cells: spontaneous killer cells directed against fresh human leukemia cells carry the VEP13 antigen. Clin Exp Immunol 58:470
7. Ziegler-Heitbrock HWL, Riethmüller G (1984) A rapid assay for cytotoxicity of unstimulated human monocytes. J Natl Cancer Inst 72:23
8. Ugolini V, Nunez G, Smith RG, Stastny P, Capra JD (1980) Initial characterization of monoclonal antibodies against human monocytes. Proc Natl Acad Sci USA 77:6764
9. Ziegler-Heitbrock HWL, Munker R, Thiel E, Krebs I, Riethmüller G (1985) Killer cell activity of human monoblastic leukemia cells as detected with a monocyte specific target cell. Blood 65:8