Role of T-Cell Antigens in the Cytolytic Activities of Large Granular Lymphocytes (LGLs) in Patients With LGL Lymphocytosis


By analyzing surface antigens and cytolytic functions of proliferating large granular lymphocytes (LGLs), three types of T cell LGL lymphocytosis were delineated. The first, most commonly encountered type exhibited CD3-4* 8* 16*. WT31* phenotype, low or undetectable non-major histocompatibility complex (MHC)-restricted cytotoxicity, and moderate to strong antibody-dependent cytotoxicity (ADCC) and lectin-dependent cellular cytotoxicity (LDCC). Because these LGLs carried T cell cytotoxicity and moderate to strong antibody-dependent non-major histocompatibility complex (MHC)-restricted cytotoxicity, it may have developed from populations of in vivo primed cytotoxic T lymphocytes with unknown antigen specificity. The second, rare type of LGL lymphocytosis exhibited CD3* 4* 8* 16*, WT31* phenotype, and strong non-MHC-restricted, ADCC and LDCC cytotoxicities. These cells were probably derived from the lymphocytes of the same phenotype found in small numbers in normal peripheral blood. Because anti-CD3 MoAb inhibited non-MHC-restricted cytotoxicity of the LGLs, a Ti not detected by WT31 MoAb, but putatively present seemed to serve as a specific receptor for target tumor cell recognition. The third type of LGL lymphocytosis showed CD3* 4* 8* 16*, WT31* phenotype, and lacked cytolytic activities and parallel tubular arrays. These LGLs probably evolved from cells with the same characteristics selectively located in the germinal centers of lymphoid tissues. Taken together, in patients with LGL lymphocytosis, T cell-associated antigens expressed on LGLs were shown to be involved in the regulation of LGL-mediated cytolytic activities. In addition, studies of surface antigens and the effects of MoAbs and lectins on cytolytic activities may be useful in clarifying the normal counterpart of LGLs from which leukemic or reactively proliferating LGLs originate.

A GROUP OF DISORDERS, collectively termed large granular lymphocyte (LGL) leukemia, LGL lymphocytosis, or Tγ-lymphoproliferative disease, is characterized by the proliferation of large lymphocytes with azurophilic granules in the cytoplasm. Proliferating LGLs usually display no or low, if any, non-major histocompatibility complex (MHC)-restricted cytotoxicity for natural killer (NK)-sensitive and NK-insensitive target tumor cell lines, but LGLs from some patients exhibit potent non-MHC-restricted cytotoxicity. LGLs of the CD3* 16*, but not of the CD3* 16* phenotype, have a tendency to exhibit such cytotoxicity. LGLs of many patients have been reported to exhibit antibody-dependent cellular cytotoxicity (ADCC), though to our knowledge it has not been reported whether proliferating LGLs also show lectin-dependent cellular cytotoxicity (LDCC).

In this report, we present the results of studies into non-MHC-restricted cytotoxicity, ADCC and LDCC of peripheral blood mononuclear cells (PBMCs) obtained from seven patients with LGL lymphocytosis, and also the roles of T cell-associated antigens in the cytolytic activities of proliferating LGLs measured using monoclonal antibodies (MoAbs) reactive with those antigens. The origin of these proliferating LGLs is discussed, based on the results of the cytolytic activity assays, surface marker analyses, ultrastructural examination, and T cell antigen receptor (Ti) gene rearrangement studies.

MATERIALS AND METHODS

Surface marker analysis. PBMCs were obtained by Ficoll-Conray density gradient centrifugation. Indirect immunofluorescence analysis was performed as described previously. The immunoglobulin G (IgG) Fc receptor of T cells (γF cells) was demonstrated by the double rosetting of sheep erythrocytes and ox erythrocytes coated with rabbit anti-ox erythrocyte IgG.

Ultrastructural examination. For ultrastructural examination, peripheral blood buffy coats were fixed at room temperature for three hours with 2% paraformaldehyde and 2.5% distilled glutaraldehye in 0.1 mol/L cacodylate buffer, pH 7.4. The specimens were then fixed at 0°C for 90 minutes in buffered 2% osmium tetroxide, dehydrated in ethanol, and embedded in Poly/Bed 812 (Poly-sciences, Inc., Warrington, PA). Ultrathin sections were double stained with uranyl acetate and lead citrate, and were observed under an electron microscope.

Analysis of Ti-β gene rearrangement. Rearrangement of the Ti-β gene was analyzed by Southern blotting. Ten micrograms of high molecular weight DNA were prepared from PBMCs, digested with EcoRI or BamHI restriction endonucleases, size-fractionated by agarose-gel electrophoresis, and transferred to nitrocellulose paper. These nitrocellulose blots were hybridized with nick-translated P-labeled DNA probes of the human Ti-β gene. The blots were washed at appropriate stringencies, and were visualized by autoradiography. The human Ti-β gene probe was a BglI/ EcoRV fragment of the cDNA clone YT1-2 that contained the C region of the Ti-β gene.

Assay for cytolytic activities. PBMCs, 1.6 x 10^5, per microwell were incubated for 20 to 24 hours in RPMI 1640 medium with 10% fetal calf serum at 37°C in humidified air containing 5% CO₂, after which time their non-MHC-restricted cytotoxicity was assayed in triplicate against 8 x 10³ ⁵¹Cr-labeled target cells in a five-hour ⁵¹Cr-release test. The effector-to-target cell ratio (E/T ratio) seemed to serve as a specific receptor for target tumor cell recognition.
ratio) was 20:1. NK-sensitive cell lines K562 and MOLT-4, and NK-insensitive cell lines Daudi, Raji, and P815 were used as target cells. After five hours incubation, the supernatant fluid was harvested, and the radioactivity determined with a gamma well counter. Specific \(^{51}\text{Cr}\) release was calculated using the following formula: percent release = ((experimental \(^{51}\text{Cr}\) release – spontaneous \(^{51}\text{Cr}\) release) / (maximum \(^{51}\text{Cr}\) release – spontaneous \(^{51}\text{Cr}\) release)) \times 100.

To assay ADCC, heat-inactivated rabbit anti-P815 serum was added at a final dilution of 1:900 to \(^{51}\text{Cr}\)-labeled P815 target cells in the cytotoxicity assay. Aspecific antibodies at this concentration did not affect the spontaneous \(^{51}\text{Cr}\) release from P815 target cells.

LDCC was assayed against \(^{51}\text{Cr}\)-labeled P815 or K562 target cells, following addition of 1:9,000-diluted phytohemagglutinin (PHA)-P (Gibco Laboratories, Grand Island, NY).

To determine the effects of MoAbs on non-MHC-restricted cytotoxicity, a final concentration of 1 \(\mu\text{g/mL}\) of sodium azide-free MoAbs OKT1 (anti-CD2), OKT3 (anti-CD3), OKT4 (anti-CD4), OKT1 (anti-CD5), and OKT8 (anti-CD8), kindly provided by Dr G. Goldstein, and a final concentration of 10 \(\mu\text{g/mL}\) of MoAb WT31 (Sanbio BV-Biological Products, Uden, The Netherlands), which reacts with the nonpolymorphic determinant of Ti-\(a/b\) chains, were added to effector PBMCs one hour before \(^{51}\text{Cr}\)-release assay. MoAbs at these concentrations were found to be optimal for induction or inhibition of non-MHC-restricted cytotoxicity in patients’ LGLs. Addition of MoAbs did not affect the spontaneous \(^{51}\text{Cr}\) release from target tumor cells.

Percentage of LGLs in lymphocytes was determined by May-Giemsa-stained peripheral blood smears.

RESULTS

Clinical features of the patients. Our patients consisted of two males and five females with a median age of 60 years at presentation, and an age range of 22 to 80 years (Table 1). All were Japanese. Patient no. 1 had congenital hypoparathyroidism, and patient no. 6 had been exposed to radiation from the atomic bomb in 1945. All had decreased percentage of peripheral blood granulocytes and increased percentage of peripheral blood LGLs. In contrast to the LGLs isolated from normal individuals, those obtained from the patients tended to exhibit fewer and smaller granules. Neither significant lymphadenopathy nor hepatosplenomegaly was detected in any of the patients. Severe anemia was noted in patient no. 6, who was thus treated with bolus methylprednisolone, but no improvement was observed. However, administration of cyclophosphamide did cause improvement. The detailed clinical features of this patient will be presented elsewhere. The other six patients had been stable for at least 1 year without any treatment.

Phenotypic, ultrastructural, and immunogenotypic analysis of LGLs. Surface marker determination revealed considerable heterogeneity (Table 2). Three broad groups could, however, be delineated. Patients no. 1 to 5 showed proliferation of LGLs with CD2\(^+\) 3'4'8'16', WT31\(^+\) phenotype. In most of these patients, the cells were also \(\gamma\delta\). Two-color staining analysis revealed that CD8\(^+\) cells were CD4\(^+\) in patient no. 4. LGL lymphocytosis with CD3'4'8' cells is the most often reported phenotype in the literature. LGLs from patient no. 6 were CD2\(^+\) 3'4'8'16', WT31\(^+\), \(\gamma\delta\), and those from patient no. 7 were CD2\(^+\) 3'4'8'16', WT31\(^+\). The presence of CD16 antigen was detected by CLB FeCRF gran 1 (VD2) MoAb, but not by Leu-11a or Leu-11c MoAb. Similar findings were reported by others. Briefly, PBMCs from normal individuals were applied to columns containing nylon wool, and eluted nylon wool-nonadherent cells were added to Percoll density gradient solutions. After centrifugation, each fraction was collected. The lymphocytes from low-density fractions 1 and 2 were mixed, labeled with either anti-CD3 MoAb OKT3 or anti-CD16 MoAb Leu-11b, and then added to goat anti-mouse Ig antibody-coated plates. The nonadherent cells (OKT3\(^-\) or Leu-11b\(^-\)) were harvested and used as effector cells for the cytotoxicity assay. The harvested CD3' lymphocytes from one donor contained 97% LGLs, 95% CD16' cells, 4% CD3' cells, and 76% Leu-7' cells, and were used as NK cells. The harvested CD16' lymphocytes contained 45% LGLs, 9% CD16' cells, 88% CD3' cells, and 38% Leu-7' cells, and were used as low-density T lymphocytes. The lymphocytes from high-density fraction 4 of Percoll solutions contained 3% LGL, 5% CD16' cells, 97% CD3' cells, and 8% Leu-7' cells, and were used as high-density T lymphocytes.

Table 1. Patient Characteristics

| Patient No. | Age/Sex | WBCa (\(\mu\text{L}\)) | Granulocytes (%) | Lymphocytes (%) | LGLs in Lymphocytes* | Hemoglobin (g/dL) | Platelets (\(\times 10^9/\mu\text{L}\)) | Lymphocytes in the Bone Marrow (%) | Physical Findings | Therapy | Clinical Course |
|-------------|---------|-------------------|-----------------|----------------|---------------------|-----------------|------------------------|-----------------|----------------|----------------|
| 1           | 22/F    | 5,500             | 14              | 81             | 77                  | 10.0            | 43                     | 14              | —              | —              | Stable for 2 yr |
| 2           | 56/M    | 21,500            | 17              | 82             | 95                  | 14.7            | 36                     | 31              | —              | —              | Stable for 2 yr |
| 3           | 60/F    | 15,000            | 4               | 92             | 95                  | 10.3            | 29                     | 36              | —              | —              | Stable for 1 yr |
| 4           | 53/F    | 12,300            | 9               | 89             | 78                  | 11.4            | 29                     | 19              | —              | —              | Stable for 1 yr |
| 5           | 69/M    | 21,000            | 23              | 74             | 99                  | 17.6            | 19                     | 22              | —              | —              | Stable for 5 yr |
| 6           | 60/F    | 5,600             | 13              | 86             | 91                  | 4.7             | 20                     | 12              | Anemia + t     | Improved t    |
| 7           | 80/F    | 13,500            | 11              | 88             | 82                  | 11.7            | 22                     | 22              | —              | —              | Stable for 11 yr |

*Percentage of LGLs in lymphocytes was determined by May-Giemsa-stained peripheral blood smears.

†Methylprednisolone pulse therapy was ineffective for anemia, while administration of cyclophosphamide improved it.
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Table 2. Phenotypic, Ultrastructural, and Immunogenotypic Analysis of Patient Blood Mononuclear Cells

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<tr>
<th>Patient No.</th>
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<th>CD5 (OKT3)</th>
<th>CD8 (OKT8)</th>
<th>CD11 (OKM1)</th>
<th>CD16</th>
<th>NKH1 (Leu-11)</th>
<th>HNK-1 (Leu-7)</th>
<th>B1</th>
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| Controls   | ±6         | ±6         | ±7         | ±5         | ±7         | ±4         | ±7         | ±6   | ±3            | ±7            |   |   |      |          |

Abbreviations: G, germ line; A, rearranged.

Table 3. Cytolytic Activities of Patient Blood Mononuclear Cells

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<th>Raji</th>
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| Controls   | ±20 | ±17   | ±14   | ±1   | ±0   | ±16  | ±13  | ±9   |

PBMCs from seven patients and six normal donors were cultured for one day, and assayed for their cytolytic activities against various target cells at an E:T ratio of 20:1. Percent cytotoxicity of fresh PBMCs against K562, MOLT-4, and Daudi target cells was 32% ± 14%, 30% ± 13% and 8% ± 3%, respectively, in normal individuals.

round nucleus with margined heterochromatin and occasional nucleoli. Cytoplasmic granules containing parallel tubular arrays (PTAs) were detected in six patients. Patient no. 7 lacked the PTAs.

Monoclonal rearrangement of the Ti-β gene was not observed in patients no. 1 and 4. PBMCs of patients no. 6 had a rearranged Ti-β gene in one allele, while those of the other patients had the rearrangement in both alleles.

Cytolytic activities of LGLs and the effects of MoAbs on the cytotoxicities. After a one-day in vitro incubation, PBMCs from the patients and six normal individuals were assayed for their non-MHC-restricted cytotoxicity, ADCC, and LDCC (Table 3). Apart from cells of patient no. 6, patients had the rearrangement in both alleles. A rearranged Ti-fl gene was not observed in patients no. 1 and 4. PBMCs of patients no. 6 had no further differences mean is not clear, but similar findings of different susceptibility were reported by others.18

The effects on non–MHC-restricted cytotoxicity of MoAbs reactive with CD2,3,4,5,8, and Ti antigens were examined (Fig 1). Addition of anti-CD3 and anti-Ti (WT31) MoAbs induced significant cytotoxicity against K562 and Daudi cells, while the cytotoxicity for MOLT-4 and Raji cells was not augmented in cells from most patients. Treatment of patient no. 6 derived PBMCs with anti-CD2 and anti-CD3 MoAbs inhibited an otherwise constitutive non–MHC-restricted cytotoxicity. Anti-CD4, 5, and 8 MoAbs had no effects on cytotoxicity (data not shown). In cultures of CD16+ NK cells isolated from normal donors, NK activity for K562, Daudi, and Raji cells was inhibited by anti-CD2 MoAb. Non–MHC-restricted cytotoxicity of low-density CD3+ T lymphocytes against K562 cells was induced by anti-CD3 and anti-Ti MoAbs, while that of high-density CD3+ T lymphocytes was not induced by these MoAbs.

Without a one-day PBMC preincubation, anti-CD3 MoAb treatment induced lower, but significant, levels of non–MHC-restricted cytotoxicity (Fig 2). Because preincubation of effector cells was not necessary for the induction of the cytotoxicity, it is clear that the assay reflected the in vivo activity of the LGLs.

Effects of rIFNs and rIL-2 on non–MHC-restricted cytotoxicity. Anti-CD3 MoAb is known to induce production of IL-2 by lymphocytes,19 as other lymphokines, such as IFN-γ, may also be produced. The possibility could not be excluded that all these subsequently enhanced non–MHC-restricted cytotoxicity. Thus, high concentrations of rIFN-α, -β, and -γ, and rIL-2 were added to one-day cultured PBMCs one hour before a 51Cr-release assay, so that their effects on non–MHC-restricted cytotoxicity could be determined. A small stimulation of cytotoxicity was observed, but it was much lower than that induced by anti-CD3 MoAb (data not shown). These results suggested that anti-CD3 MoAb-induced non–MHC-restricted cytotoxicity was not mediated by IFNs or IL-2 produced from the lymphocytes during culture.
restricted cytotoxicity for K562 and Daudi target cells was induced by addition of anti-CD3 and anti-Ti MoAbs. It is known that antigen-specific, MHC-restricted, cytotoxic T lymphocyte (CTL) clones, noncytolytic proliferating T cell clones, and freshly isolated normal CD3-, Leu-7- cells of LGL morphology can be triggered to exhibit non–MHC-restricted cytotoxicity against NK-sensitive and NK-insensitive target cells by treatment with anti-CD3 MoAbs and certain lectins. This was corroborated in the present study. Thus LGL leukemia cells and reactively proliferating LGLs already possess the lytic machinery necessary for the destruction of target cells. CD3-, Leu-7- LGLs, present in normal peripheral blood, which have the capacity to mediate anti-CD3 MoAb-induced non–MHC-restricted cytotoxicity and LDCC are suspected to be in vivo primed CTLs, possibly active against virus-infected cells. LGLs of most of our patients carried Ti, and treatment with anti-Ti, anti-CD3, and PHA elicited non–MHC-restricted cytotoxicity. Thus, these LGLs may also have developed from populations of in vivo primed CTLs with unknown antigen specificity.

LGLs of patient no. 6 expressing a unique CD3+4+8-, WT31- phenotype constitutively exhibited non–MHC-restricted cytotoxicity, which could be inhibited by anti-CD2 and anti-CD3 MoAb treatment. Anti-CD2 MoAb probably inhibited an antigen-independent conjugate formation between CD2 antigen on the effector lymphocytes and lymphocyte function-associated antigen-3 (LFA-3) on the target tumor cells. The mechanism of anti-CD3 MoAb-mediated suppression needs a different explanation. Mingeon et al. have recently reported CD3+, WT31- cell lines with Ti- chains; MoAb generated against the clonotypic structure of the Ti- chains, as well as anti-CD3 MoAb, blocked the cell lines’ non–MHC-restricted cytotoxicity. Borst et al. and Brenner et al. have also reported CD3-, WT31- cell lines with CD3/Ti- complex whose non–MHC-restricted cytotoxicity was inhibited by anti-CD3 MoAbs. Herrcnd et al. reported CD3+8-, WT31+, NKH-1+ cell lines whose non–MHC-restricted cytotoxicity was blocked by anti-CD3 MoAb and a MoAb that was generated against clonotypic determinants of these clones. Based on the fact that, in antigen-specific CTL clones, antigen-specific cytotoxicity is blocked by MoAbs directed against Ti clonotypic structures and by MoAbs directed against CD3 antigen, the above findings suggest that clonotypic structures of Ti- and Ti- chains are directly involved in non–MHC-restricted cytotoxicity, and act as a specific receptor for target tumor cell recognition. Accordingly, anti-CD3 MoAb-mediated inhibition of non–MHC-restricted cytotoxicity in patient no. 6 also indicates the same possibility, i.e., that a Ti not detected by WT31 MoAb, but putatively present serves as a specific receptor for target tumor cell recognition.

In most of our experiments, while non–MHC-restricted cytotoxicity against K562 and Daudi target cells was induced by anti-CD3 and anti-Ti MoAbs, cytotoxicity against MOLT-4 cells was not induced. K562 and Daudi cells bear Fc receptors for mouse IgG, whereas

**DISCUSSION**

After a one-day incubation of lymphocytes, MoAbs reactive with T cell-associated CD2, 3, 4, 5, 8, or Ti antigens were added one hour before a 51Cr-release assay (Fig 1). Except for cells of patient no. 6, which exhibited constitutive non–MHC-restricted cytotoxicity, patient PBMCs non–MHC-restricted cytotoxicity for K562 and Daudi target cells was induced by addition of anti-CD3 and anti-Ti MoAbs. It is known that antigen-specific, MHC-restricted, cytotoxic T lymphocyte (CTL) clones, noncytolytic proliferating T cell clones, and freshly isolated normal CD3-, Leu-7- cells of LGL morphology can be triggered to exhibit non–MHC-restricted cytotoxicity against NK-sensitive and NK-insensitive target cells by treatment with anti-CD3 MoAbs and certain lectins. This was corroborated in the present study. Thus LGL leukemia cells and reactively proliferating LGLs already possess the lytic machinery necessary for the destruction of target cells. CD3-, Leu-7- LGLs, present in normal peripheral blood, which have the capacity to mediate anti-CD3 MoAb-induced non–MHC-restricted cytotoxicity and LDCC are suspected to be in vivo primed CTLs, possibly active against virus-infected cells. LGLs of most of our patients carried Ti, and treatment with anti-Ti, anti-CD3, and PHA elicited non–MHC-restricted cytotoxicity. Thus, these LGLs may also have developed from populations of in vivo primed CTLs with unknown antigen specificity.

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**Fig 1.** Non–MHC-restricted cytotoxicity, and the effects of MoAbs on the cytotoxicity. PBMCs from seven patients, and NK cells and high- and low-density T lymphocytes from three normal individuals were incubated for one day, and then assayed for their cytolytic activities with and without the addition of 1 μg/mL of anti-CD3 MoAb OKT3. E:T ratio was 20:1.

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<th>Patient No.</th>
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**Fig 2.** Non–MHC-restricted cytotoxicity of fresh v one-day cultured PBMCs. Fresh and one-day cultured PBMCs were assayed for their cytolytic activities with and without the addition of 1 μg/mL of anti-CD3 MoAb OKT3. E:T ratio was 20:1.
ROLE OF T-CELL ANTIGENS IN LGL CYTOTOXICITY

MOLT-4 cells do not, suggesting that cross-linking of CD3 or Ti antigen on the effector lymphocytes with Fc receptors on the target tumor cells through anti-CD3 or anti-Ti-reactive MoAbs is involved in triggering nonspecific lytic machinery in the effector cells. Indeed, the addition of anti-CD3 MoAb caused cross-linking of LGLs and targets and subsequent cell damage when examined by electron microscopy (manuscript in preparation).

It has been shown that IL-2 is secreted when lymphocytes are cultured with anti-CD3 MoAbs. This raised the possibility that anti-CD3 MoAb-induced patient LGL non-MHC-restricted cytotoxicity was mediated by IL-2 or other lymphokines produced during short-term culture with anti-CD3 MoAb. This possibility, however, seems unlikely, since the lymphokines, IL-2 and IFNs, though known to enhance non-MHC-restricted cytotoxicity, when added to effector lymphocytes at high concentrations did not induce high levels of cytotoxicity. Furthermore, the one-hour incubation period before the \(^{51}\text{Cr}\)-release assay was probably too short to allow production of adequate lymphokine concentrations. Loughran et al. reported that incubation of leukemic LGLs with anti-CD3 MoAb for more than one day augmented their non-MHC-restricted cytotoxicity, whereas addition of the MoAb to freshly isolated PBMCs at the start of a four-hour \(^{51}\text{Cr}\)-release assay caused no stimulation. They did not preincubate LGLs for one day in the absence of anti-CD3 MoAb, and this is the probable reason why they could not induce effector lymphocyte cytotoxicity by a short-term incubation with anti-CD3 MoAb. Although it is highly possible that they and we have found the same anti-CD3 MoAb-induced cytotoxicity phenomenon, their experimental system raises the possibility that lymphocytes incubated for one or more days with anti-CD3 MoAb might have produced lymphokines that subsequently enhanced the non-MHC-restricted cytotoxicity.

It is not known why the cytolytic activities were enhanced by simply preincubating effector lymphocytes for one day (Fig 2). Similar findings have been reported for normal NK cells, and leukemic LGLs. Cytophilic IgG, which may inhibit the lytic activity of NK cells in vivo, might be released from NK cell surfaces after a short period in vitro culture, thus enhancing the in vitro cytotoxicity. When patient’s LGLs were incubated for one day at 37°C, they developed potent non-MHC-restricted cytotoxicity. It is possible that IgG in the patient’s serum inhibited in vivo and early in vitro expression of the cytotoxicity.

In normal individuals, purified NK cells showed strong cytotoxicity for NK-sensitive and NK-resistant target cells (Fig 1). This is explained by the fact that NK activity is regulated by monocytes, and after their depletion, NK cells exhibit strong cytotoxicity even for NK-resistant target cells. NK activity for K562, Daudi and Raji cells, but not for MOLT-4 cells, was inhibited by anti-CD2 MoAb treatment (Fig 1). Anti-CD2 MoAb treatment is known to inhibit NK function probably by inhibition of an antigen-independent conjugate formation, as discussed previously. No inhibition of anti-MOLT-4 NK activity by anti-CD2 MoAb treatment may be explained by the inability of CD2 antigen to recognize MOLT-4 target cells or by the defective expression of LFA-3 on MOLT-4 cells. Further investigation is required. Anti-CD3 and anti-Ti MoAb-mediated induction of anti-K562 cytotoxicity in normal low-density T lymphocytes (Fig 1) may be mediated by T lymphocytes expressing Leu-7 antigen and LGL morphology as was reported by Phillips and Lanier.

Finally, the normal cell lineage from which leukemic or reactively proliferating LGLs originated are discussed. CD3\(^{+}\), Leu-7 antigen and LGL morphology as was reported by Phillips and Lanier.26

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Role of T-cell antigens in the cytolytic activities of large granular lymphocytes (LGLs) in patients with LGL lymphocytosis

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