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Normal and Neoplastic Lymphocyte Maturation

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Lymphocytes are cells that are responsible for processes of specific antigen recognition and for those aspects of the immune response that characterize adaptive immunity. In this respect adaptive immunity can be characterized as antigen-induced immune *memory* and *effector* functions as compared to native immunity – the nonspecific phagocytic and humoral protective elements in lower vertebrates. In vertebrates both B and T lymphocytes apparently express self-synthesized receptors that 1) are involved in the recognition of antigens, and 2) mediate the interactions between various important cells in the hematolymphoid system. There are three major subclasses of T lymphocytes – those involved with helper/inducer functions, those involved with suppressor functions, and those involved in direct cytotoxicity of antigenic target cells [1, 2].

IMMUNOGENETICS OF T CELL RECOGNITION AND FUNCTION

A major advance in the understanding of T lymphocyte classes, T lymphocyte function, and T lymphocyte recognition developed through the combination of immunogenetics and cellular immunology by Cantor and Boyse and by Zinkernagel and Doherty [3, 4]. The general case could be stated as follows: Both killer and suppressor T lymphocytes are cells that express high concentrations of the T cell markers Lyt-2,3, whereas inducer lymphocytes express high concentrations of the marker Lyt-1, with no apparent expression of Lyt-2,3. Inducer lymphocytes recognize allogeneic cells expressing MHC I region markers, or recognize foreign antigens in the context of self I region markers, whereas cytotoxic T cells recognize allogeneic cells via MHC K/D markers, or foreign antigens in the context of self K/D surface glycoproteins [3, 4]. Thus a triad of markers and properties seem to go together – cell function, cell surface Lyt expression, and the portion of the MHC region recognized by antigen-reactive T cells. Exceptions to this triad have been sought extensively, and current evidence indicates an absolute correlation between Lyt type and the type of MHC gene product the T cell recognizes (I or K/D), rather than a correlation between function and either of the two markers described above.* This implies that the Lyt molecules

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are involved somehow in the recognition process rather than the functional property of the cell that bears them, and that the generality of the triad reveals the most probable associations, presumably via selective processes of antigen-independent and/or antigen-dependent T cell proliferation and survival.

There is a second important principle involved in T lymphocyte recognition of antigen: Most T lymphocytes are G_0 small cells which are only brought into cycle upon appropriate recognition of antigen. The following is a model of antigen-induced T cell blastogenesis and T cell cooperation: Small G_0 Lyt 1 cells, which recognize I region antigens on the surface of the antigen-presenting or stimulating cell, enlarge to become cycling large lymphoblasts, and release lymphokines such as T cell growth factor (TCGF, also called Interleukin 2 [IL2]), a substance which maintains proliferation in several other subclasses of T lymphocytes, including some (if not all) Lyt-2,3 cells [5–7]. Small G_0 Lyt-2 cells recognize H-2-K/D antigens, enlarge, and begin to express surface receptors for TCGF-IL2. Their continued proliferation may be growth-factor-dependent and antigen-independent [5–7]. Thus antigen recognition is necessary for the *initiation* of Lyt-2 cell division, but is not required for *maintenance* of proliferation by these cells. Lyt-2 effector lymphoblasts of the killer cell series next use their *antigen recognition apparatus* to bind to antigenic target cells, which they subsequently lyse [1]. We have demonstrated that anti-Lyt-2 monoclonal antibodies block the two antigen recognition phases of Lyt-2 cell function -- the initial blastogenesis (but not TCGF-dependent proliferation) and the recognition phase necessary for cytolysis of antigenic target cells [8]. Similarly, anti-Lyt-1 may affect the recognition of antigen by Lyt-1 cells, although in this case the monoclonal anti-Lyt-1 antibodies augment rather than inhibit antigen-dependent blastogenesis by these cells [9].

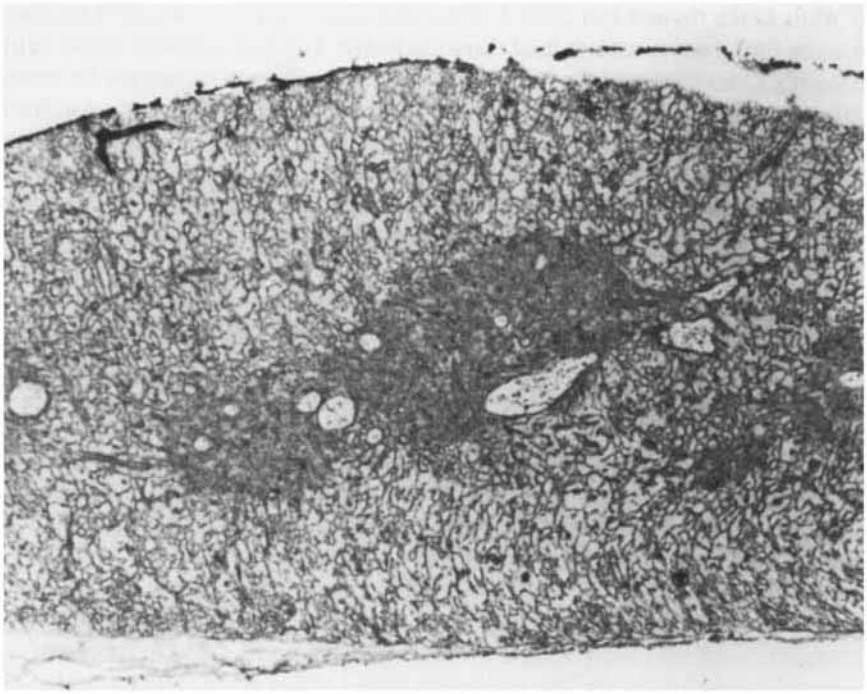
DEVELOPMENT OF IMMUNOCOMPETENT SUBCLASSES OF T LYMPHOCYTES OCCURS IN THE THYMUS

Several experiments indicate not only that the thymus is the site of maturation of immunocompetent T cells from immunologically incompetent hematopoietic precursors [2], but also that specific recognition of self-MHC markers utilized by T lymphocytes for corecognition of antigen and antigen-bearing stimulator/target cells is also a property that is developed, or selected for, within the thymus [10, 11]. The precursors of thymocytes reside originally in the yolk sac [12], but are produced throughout life within the bone marrow from a relatively infrequent subset of precursors [13]. Within the thymus, the primitive lymphoblasts reside mainly under the capsule in the thymic outer cortex, and these provide precursors of all Lyt-defined subpopulations of thymocytes and peripheral T cells [14, 15, 16]. The most frequent progeny of these outer cortical lymphoblasts are cortical small T lymphocytes, which are mainly immunologically incompetent, most of which appear to die in situ within 3–5 days after their appearance [17]. A small proportion of immunocompetent virgin T lymphocytes either enter the medulla, or emigrate to peripheral lymphoid organs [15, 17]. About 70% of emigrating cells in the mouse throughout life are Lyt-1^+, Lyt-2^-,3^-, the other 30% or so expressing high levels of Lyt-2,3 and low levels of Lyt-1 [16, 18]. Study of the outer cortical thymocytes suggests that these surface marker-defined lymphocyte subclasses may be separate lineages throughout their thymic existence, from the primitive lymphoblasts in the outer cortex through the small lymphocytes in the deep cortex and the virgin T cells in the medulla and in the periphery [16].

While in the thymus (for their 3–5-day maturation/selection sojourn) thymic lymphocytes come into contact with at least three distinctive types of relatively sessile cells. In the outer cortex a rare subpopulation of thymic epithelial cells may be marked by transcapsular staining with fluorescein isothiocyanate [16, and a personal communication from B. Kyewski]. The cells so marked have been described elsewhere as "nurse" cells because they are in tight association with thymic lymphoblasts when prepared in suspension [19]. These nurse cells express the MHC markers of both K/D and I regions. The relationship of these nurse cells to the dendritic epithelial cells scattered throughout the cortex needs further study. As developing thymic lymphocytes filter down through the thymic cortex (as G_0 small thymocytes), they pass through a dendritic array of membranous processes from *cortical thymic epithelial cells;* these cortical dendritic epithelial cells express high levels of I-region products of the MHC [20]. Figure 1 shows such a field of cells stained with the monoclonal anti $I\text{-}A^k$ antibody. Because these cells express, for the most part, only low-to-undetectable levels of allotypic determinants of the H-2K and H-2D regions, they may be unique among all other cells in the body in terms of this peculiar expression of I-region MHC gene products. It has been reported [21] that this class of cells contains populations of cells that produce and secrete thymopoietin, a polypeptide hormone believed to be involved in thymic lymphocyte maturation and/or proliferation. Thymic lymphocytes passing through the interstices of these dendritic processes may collect in large pools traversing the corticomedullary junction, and come into contact in that region with macrophages expressing both I-region and K/D-region MHC antigens [22]. In the medulla are more *spatulate epithelial cells,* also expressing both I-region and K/D-region MHC markers. It should be noted that infrequent dendritic epithelial cells in the thymic cortex also express allotypic determinants detected by anti-J-region antibodies [20]. The emigration site of lymphocytes from the thymus is believed to be in the region of the corticomedullary junction; and a possible graveyard for the thymocytes that die appears to be in the medulla in structures called Hassall's corpuscles. Those thymic lymphocytes destined to die appear to have an aberrant expression of H-2K region markers [24]. We have proposed elsewhere that subclasses of thymic epithelial cells are involved in the maturation and proliferation of, and selection for lymphocytes expressing receptors directed to their expressed MHC markers, and that the frequency of emigrating Lyt-1 vs Lyt 1,2,3 lymphocytes mirrors somewhat the abundance of MHC I vs K/D markers on thymic epithelial cells [20].

NEWLY DEVELOPING T AND B LYMPHOCYTES EXPRESS SURFACE RECEPTORS THAT GOVERN THEIR MIGRATION AND LOCALIZATION IN THE PERIPHERY

Emergent virgin B and T lymphocytes enter the blood stream and quickly migrate to peripheral lymphoid organs in a process involving 1) recognition of and binding to the surface of a specialized subclass of postcapillary endothelial cells, called high endothelial venule cells (HEV); and 2) subsequent migration through the vessel wall into surrounding lymphoid tissue [25–27]. The expression of receptors for these highly specialized endothelial cells is a property of mature lymphocytes that is not shared by their immature bone marrow and thymocyte precursors, or by nonlymphoid blood cells [28–30]. The in vivo process of lymphocyte binding to HEV, and subsequent transvascular migration, is outlined in Figure 2A. Figure 2B demonstrates that this cell-cell interaction can be studied in vitro in a model system, described originally by Stamper and Woodruff [28], in which lymphocytes bind specifically to HEV during incubation on frozen sections of murine lymph nodes or Peyer's patches. By quantitating the binding ability of various lymphocyte



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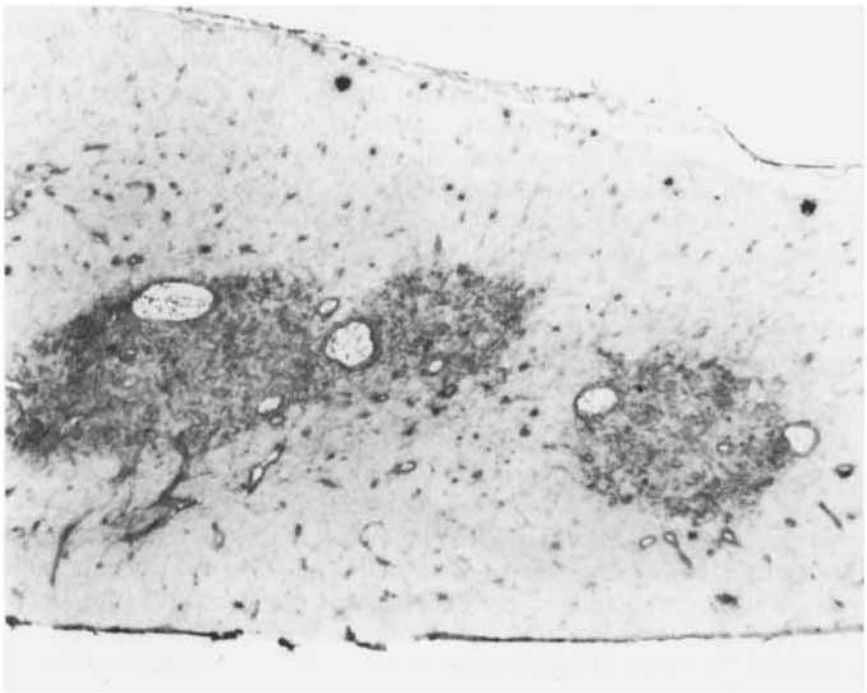


B

Fig 1 C57B1/6-H-2^k mouse thymus stained with A) monoclonal anti-I-A^k and B) monoclonal anti-H-2-K^k Both antibodies produce confluent medullary staining, but only I A is expressed on dendritic cortical cells

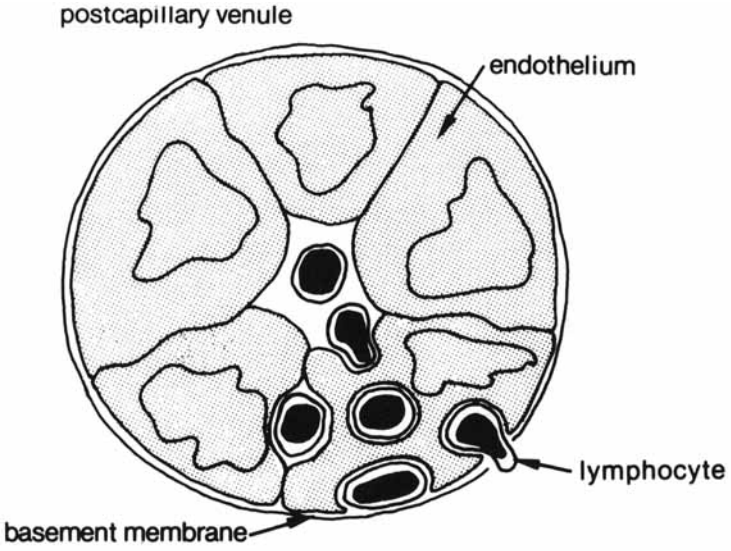


Fig. 2A. Diagrammatic cross section of a lymph node postcapillary venule. Small dark cells are lymphocytes adhering to and migrating across the specialized endothelial walls of these vessels. (Redrawn from J.L. Gowans, Hosp Pract 3(3):34, 1968.

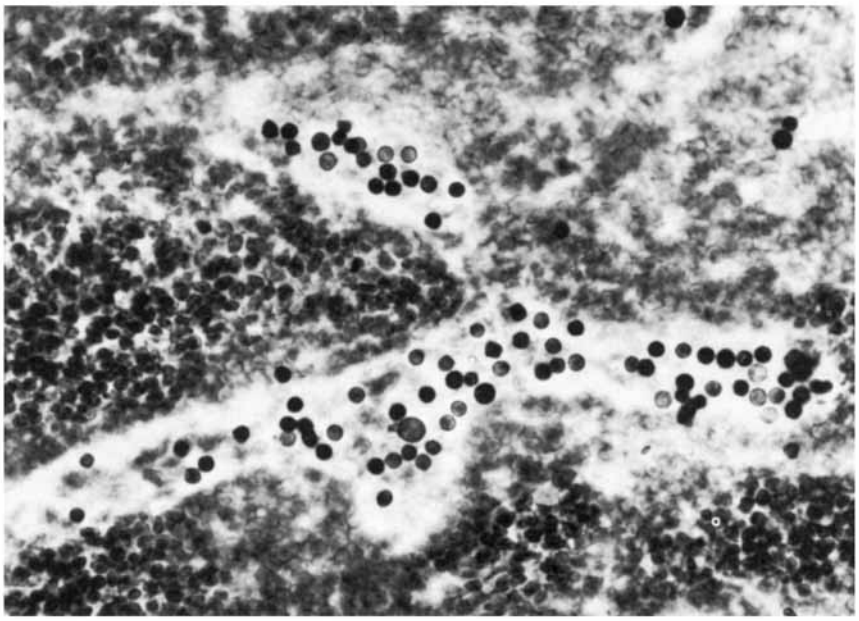


Fig. 2B. Lymphocytes (dark, round cells) bound to a transected high-endothelial venule in a lymph node frozen section after in vitro incubation.

populations in this in vitro system [29, 31], we have gained some insight into the evolution of this cell-cell interaction, and some understanding of its importance in directing lymphocyte traffic. Figure 3 demonstrates that the ability of lymphocytes from various

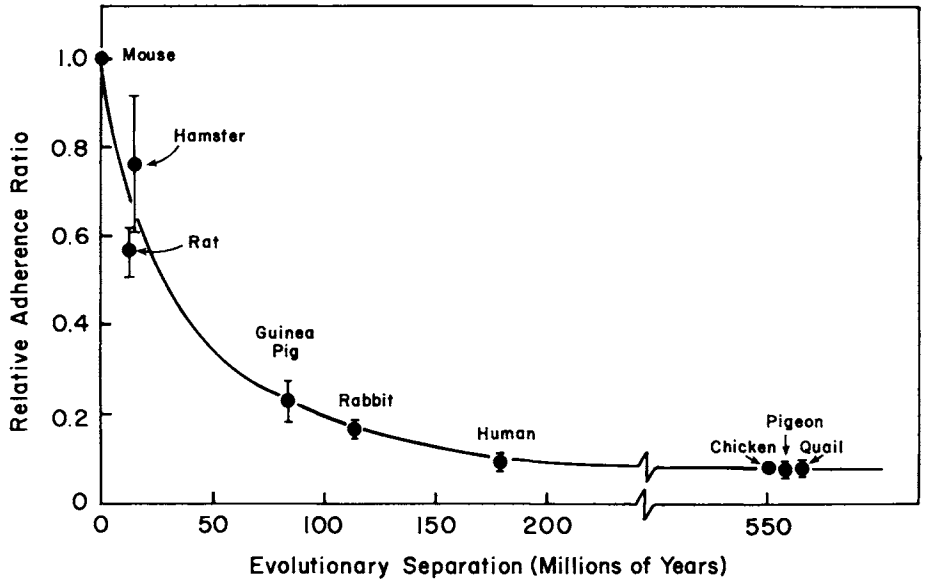


Fig. 3. Species specificity of in vitro adherence to mouse mesenteric node HEV.

vertebrate species to bind to mouse HEV declines exponentially with the evolutionary distance separating the lymphocyte donor from the mouse host. We have interpreted this as evidence for continuous coevolution of the lymphocyte and endothelial cell recognition elements [31, 32]. Not only is there a progressive evolutionary divergence between species, but there are also detectable variations in HEV-binding properties of lymphocytes within each species: We have defined one major difference in the HEV-binding characteristics of BALB/c and C57BL lymphocytes, and have mapped this trait to a single region on chromosome 7 [31]. Whether this genetically defined difference is due to an allotypic variant of the lymphocyte recognition molecule(s) for HEV is currently unknown. In addition to these interspecies and interstrain differences, evolutionary pressures have resulted in the existence of more than one set of complementary lymphocyte and HEV recognition receptors or elements *within* each lineage, apparently to direct lymphocyte migration through particular regions of the body. For instance, selective lymphocyte migration through the gut-associated Peyer's patches or through the gut-independent peripheral lymph nodes is well documented [33–40]. We have demonstrated the existence of distinct recognition determinants on HEV in Peyer's patches and peripheral lymph nodes, and have argued that the selective expression of receptors for these endothelial determinants by various lymphocyte populations is a major factor controlling their circulation through these sites [30–39]. Our experiments have defined two distinct kinds of organ-specific homing by lymphocytes: 1) Normal small lymphocyte populations demonstrate limited organ specificity of migration based on lymphocyte class. For instance, peripheral node high endothelial cells bind T cells in preference to B cells, whereas Peyer's patch HEV cells select about twice as many B cells as T cells. These relative homing preferences of B and T cell populations are observed regardless of their organ of origin. It is interesting that the class-specific binding preferences of peripheral node and Peyer's patch HEV are closely correlated with (and thus may well determine) the fractional representation of B and T

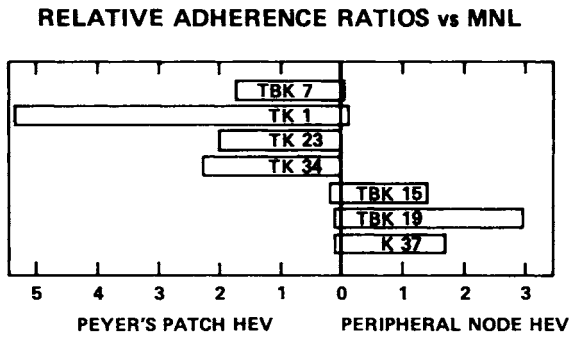


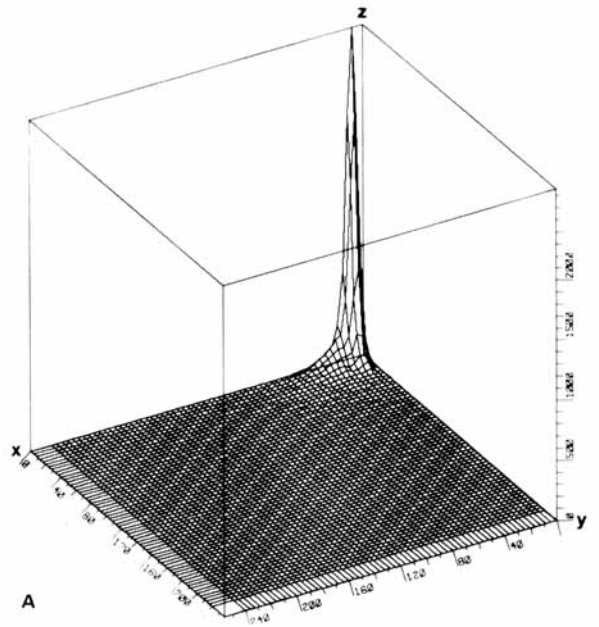
Fig. 4. Organ specificity of in vitro adherence of lymphomas to HEV in peripheral (axillary and brachial) nodes and Peyer's patches. The adherence of normal syngeneic mesenteric node lymphocytes to HEV in either organ is defined as unity.

lymphocyte populations in the two organs (S.K. Stevens, I.L. Weissman, and E.C. Butcher, in preparation). 2) Some lymphocyte subpopulations may demonstrate nearly absolute organ specificity of homing, or of HEV recognition, as exemplified by certain neoplastic T cells and their (presumably clonal) progeny, which bind exclusively or nearly exclusively to either Peyer's patch HEV, or peripheral node HEV (Fig. 4) [31, 41]. These T cell lymphomas are of thymic origin, and apparently are committed to organ-specific homing prior to their exit from the thymus [30]. This observation suggests either a) that normal thymocytes, from which these lymphomas derive, may themselves be precommitted to future expression of a particular HEV receptor, or b) that the process of neoplastic transformation and blastogenesis may nonspecifically induce organ-specific homing receptors, perhaps in imitation of a normal differentiative process associated with antigen-induced blastogenesis in the periphery. Finally, the exciting possibility exists that the metastatic potential of these tumors may be determined in part by their particular lymphoid organ HEV receptors.

RECEPTOR-MEDIATED PROLIFERATION OF NORMAL AND NEOPLASTIC T LYMPHOCYTES

In the first section, we outlined some of our evidence that proliferation of T lymphocytes (and perhaps B lymphocytes) appears to be governed largely by recognition of antigen by antigen-specific cell surface receptors linked to cell surface receptor-mitogen complexes. Several years ago we proposed the hypothesis that lymphomagenesis by oncogenic retroviruses was controlled by misregulation of or uncontrolled stimulation of these cell surface receptor-mitogen complexes [42–44].

Briefly, we proposed that oncogenic retroviruses bind to that subset of normal lymphocytes bearing antigen-specific receptors directed against retroviral envelope moieties. The retroviruses thus bound might infect the lymphocyte leading to cellular production of more retrovirus envelope structures. In turn, this could lead to receptor-mitogen complex stimulation of progeny cells into several (and perhaps endless) rounds of division. Using a sensitive virus-binding assay we showed that, indeed, each T lymphoma induced by a particular retrovirus bears surface receptors specific for the virus that induces it (Fig. 5). At least 20 T and 1 B lymphoma bear receptors specific for the viruses they produce and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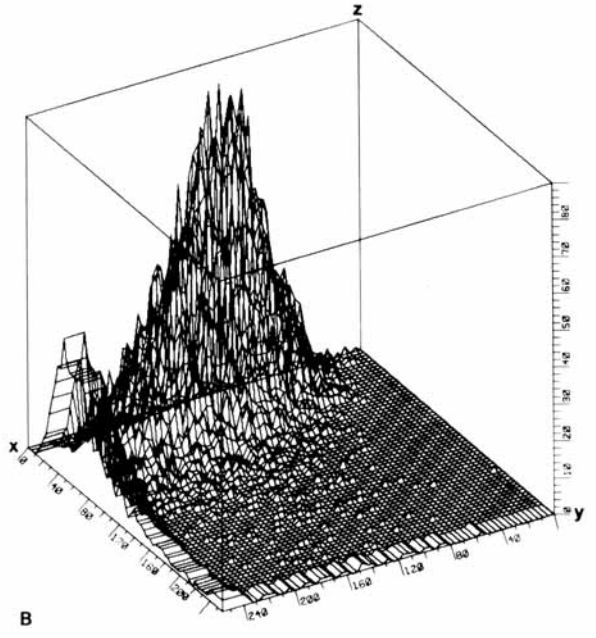
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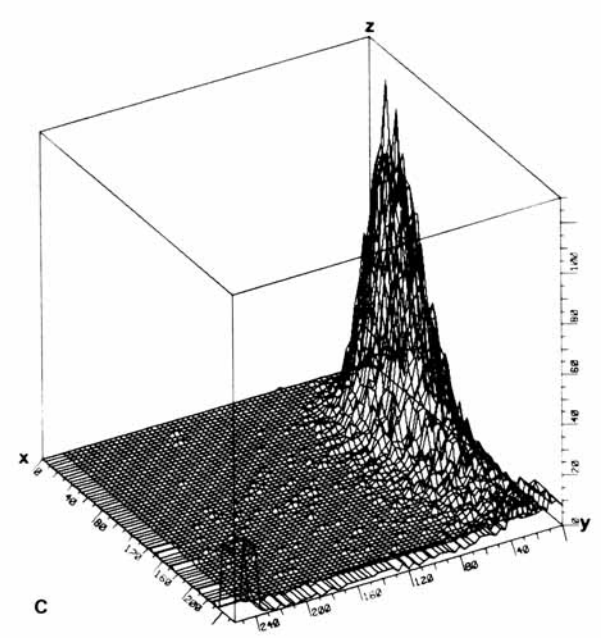

Fig. 5. Two-color FACS analysis: MCF-247 and RadLV/VL$_3$ binding specificites. These three-dimensional perspective plots show rhodaminated MCF-247 and fluoresceinated RadLV/VL$_3$ binding to three different target cell populations. MCF-247-binding increases along the X axis, fluoresceinated RadLV/VL$_3$-binding increases along the Y axis, and the frequency of cells binding a particular level of fluorescence increases along the Z axis. In each case, 10^5 cells were analyzed, and the fluorescein and rhodamine backgrounds were equal to 30 units. A) 10^6 One-week-old AKR/J thymocytes were incubated simultaneously with 0.2 A_{260} unit of fluoresceinated RadLV/VL$_3$ and 0.2 A_{260} unit of rhodaminated MCF-247. Virus-binding assay was performed as previously described [44], and two-color binding was assessed by the FACS. B) 10^6 KKT-1 cells were assayed for simultaneous binding of fluoresceinated RadLV/VL$_3$ and rhodaminated MCF-247 as in (A). C) 10^6 BL/VL$_3$ cells were assayed for simultaneous binding of fluoresceinated RadLV/VL$_3$ and rhodaminated MCF-247 as in (A). Cells with fluorescence greater than 250 units, representing < 5% of all cells analyzed, were collected and combined in the 250-unit computer channel, as represented by the ridges along the distal edges of the three-dimensional plots. All data were plotted by a Calcomp plotter interfaced with a PDP-11 computer using the MAINSAIL computer program designed by W. Moore, Stanford University.

which presumably induced them [45–47]. This receptor-binding assay is extremely sensitive, and with the use of the fluorescence-activated cell sorter (FACS) we have been able to detect and transfer incipient lymphoma cells within the thymus of otherwise apparently healthy hosts; morphologically identical non-virus-binding thymic lymphocytes in the same thymus are not capable of transferring autonomously replicating lymphoma cells [44].

An important postulate of this hypothesis is that interference with receptor-virus interaction should lead to the inhibition of proliferation by these T lymphoma cells. Accordingly, we raised several types of monoclonal antibodies directed against lymphoma cell surface markers, and found four that blocked the binding of virus to lymphoma cell surfaces, whereas several others bound to the lymphoma cell surface but did not block virus binding. Those monoclonal antibodies that block virus binding also block proliferation of T lymphoma cells, either in the first G_1 cell cycle phase after addition of antibodies, or in the second round of cell division [48] (Fig. 6). Inhibition of lymphoma cell prolifera-

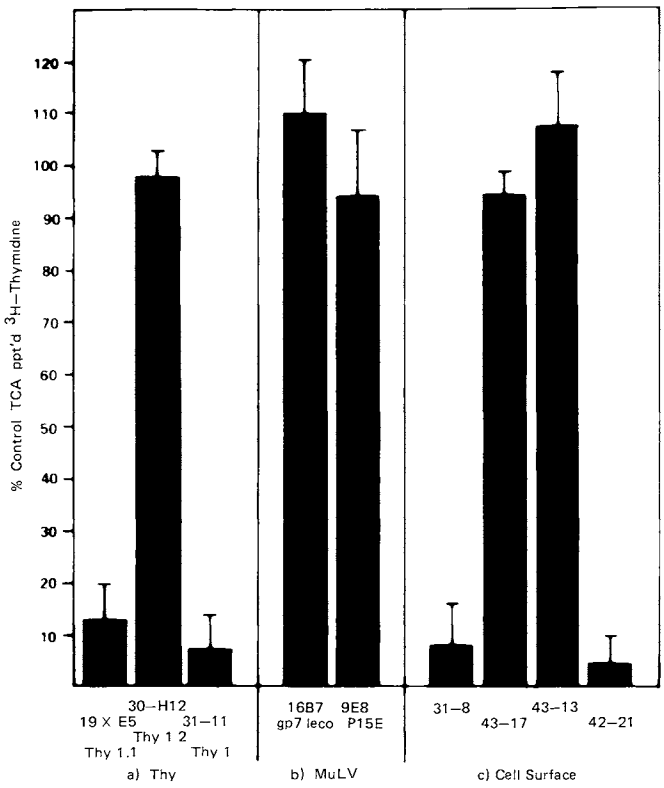

Fig. 6. Lymphoma cell growth inhibition assay. KKT-2 lymphoma cells were pelleted from subconfluent cultures and were resuspended in serum-free growth medium (MEM, GIBCO) for 2 h at 37°C at a density of 10^5 cells/ml. After repelleting, the cells were resuspended in cold tissue culture medium (MEM, 5% FCS) at a density of 2×10^4 cells/ml. Two and one-half milliliters (5×10^4 cells) were placed in the bottom of 25 cm^2 Corning tissue culture flasks and monoclonal antibody was added for a 1:12 final dilution. After growing for 14 h at 37°C, 0.1 ml of medium containing 10 μCi [^{3}H]-thymidine (NEN) was added to each culture for 2 h. Labeled cells were washed, 5% TCA was precipitated, and percent growth inhibition was calculated using cells without antibody as equal to 100% growth, KKT-2 cells were tested for growth inhibition with a) anti-Thy 1 (19 X E5, 30–H12, 31–11), b) anti-MuLV (16B7, 9E8), and c) anti-cell-surface antibodies (31–8, 43–17, 43–13, 42–21). The above data represent five experiments ± standard deviations. Monoclonal antibody 42–21 has subsequently been shown to react with Thy-1 determinants.

tion by these monoclonal antibodies could be prevented by prebinding to the lymphoma cell the oncogenic retrovirus that induced the tumor (Fig. 7). Analysis of the molecules detected by these monoclonal antibodies reveals that they are not the actual virus receptors, but are molecules (such as Thy-1) that are in great abundance on the T lymphoma cell surface. Inhibition of virus binding in these instances is probably due to steric, rather than competitive, inhibition. We proposed that the monoclonal antibodies act via inhibition of a receptor-mitogen complex that is normally activated and reactivated by binding of intact (but not necessarily infectious) retrovirus. If this is a parallel to the antigen-induced activation of T cell proliferation noted above, then it is possible that these retroviruses bind to and activate via either the antigen-specific T cell receptors or via some cell-surface entity involved in the receptor-mitogen complex.

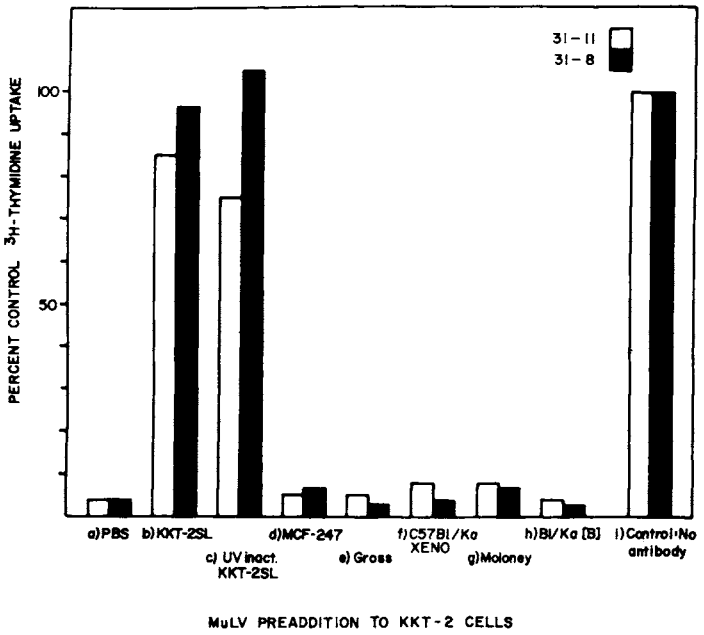

Fig. 7. The standard KKT-2 cell growth inhibition assay as outlined in Figure 6 was carried out with 31–11 and 31–8 antibodies at a 1:250 dilution on 5 × 10^4 KKT-2 cells after preincubation with purified retroviruses. One one-hundredth A_{260} unit of Sepharose-4B-purified virus [50] in 0.3 ml of PBS was incubated with KKT-2 cells for 60 min at room temperature prior to addition of inhibitory antibodies. This amount of virus represents a receptor saturation level as previously determined [45]. The origin of each retrovirus population has also been previously described [43–45]. Sepharose-4B-purified KKT-2-SL virus was also UV inactivated and used to inhibit antibody-induced KKT-2 cell growth inhibition. Five milliliters of virus in PBS (1 A_{260} unit/ml) was irradiated for 145 sec at 4,000 erg/mm^2 prior to use.

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