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MINIREVIEW

Homing Receptors as Functional Markers for Classification, Prognosis, and Therapy of Leukemias and Lymphomas (41933)

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Nonrandom Spread of Metastases (Organ Specific Metastasis). The ability of certain tumors to reproducibly colonize particular organs is a well-documented occurrence in cancer biology. The nonrandom nature of this colonization is known as organ specific metastasis (OSM) (1, 2). Metastasis is defined as the spread and growth of tumor cells. The process of metastasis is sequential, and involves tumor cell arrest in capillary beds, penetration into the parenchyma of an organ, and the proliferation of those tumor cells. The seed–soil hypothesis proposed by Paget in 1889 (3) was that, while seeds may be scattered evenly over a wide area, only those supplied with the necessary conditions and nutrients will grow and survive. The receptor–acceptor hypothesis (1, 2) attributes the specific arrest of tumor cells to the specific interaction of receptors on the tumor cell surface with acceptor molecules on the target organ (or vice versa). However, even if tumor cells arrest in capillary beds but do not penetrate the parenchyma and proliferate, metastasis would not occur. Indeed, tumor cells may reach many organs (1) but may only complete the metastatic cascade in some.

The study of OSM has expanded rapidly since the first isolation of metastatic variants by Fidler (4). This method utilized alternating *in vivo/in vitro* selections of tumor variants which were repeated until a substantial increase in the organ specific metastatic ability of the cell line was achieved. This basic protocol has now been repeated for a variety of tumor systems in a number of species. The use of selected metastatic variants has been very informative for a better understanding of tumor cell heterogeneity in many respects but has not yet unraveled the mechanism of organ specific metastasis. In the present communication we suggest that specific cell surface receptors on leukemia and lymphoma cell variants might at least partially determine the pattern of metastatic spread and that these receptors might serve as more meaningful markers for the classification, prognosis, and even treatment of lymphomas and leukemias.

Clinical Parameters of Lymphoid Malignancies. Current classifications of leukemias and lymphomas are based largely on cell morphology, cell surface markers, and organ involvement (5–7). While the general clinical features of the various leukemias may be similar, differences in specific laboratory parameters, the response to therapy, and the prognosis are apparent. Several examples serve to illustrate this principle (Table I). Acute lymphatic leukemia (ALL) is always characterized and diagnosed by the presence of bone marrows with dense accumulations of leukemia cells which often lead to severe bone marrow insufficiency. Approximately 50% of the patients have leukocyte blood counts less than 5000/mm^3 and only about 20% have more than 50,000/mm^3. While non-T, non-B, as well as B-ALL show preferential growth in the bone marrow, T-ALL usually demonstrate extra bone marrow involvement. Clinical features of acute nonlymphocytic leukemias are very similar to those of ALL. In contrast, in chronic leukemias a transient leukemic proliferation occurs in the bone marrow, but little accumulation of leukemic cells occurs, and primary bone marrow insufficiency is rare. Instead, high blood counts (often >100,000/mm^3) representing all forms of more mature or lymphocytic and myeloid cells and gross hepatosplenomegaly often result.

T-Cell lymphomas may present yet another distinctive characteristic pattern. For example,

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TABLE I. SELECTED EXAMPLES OF GROWTH OF HUMAN LYMPHOCYTIC LEUKEMIAS OR LYMPHOMAS IN VARIOUS TISSUES

	Cell marker	Bone marrow	Spleen	Liver	Lymph node
Acute lymphocytic leukemia	0	++++	++	+	+
Acute lymphocytic leukemia	T	++++	+	+	++++
Acute lymphocytic leukemia	B	++++	++	+	++
Prolymphocytic leukemia	B	++++	++++	++	−
Chronic lymphocytic leukemia	B	+	++++	++++	++++
Small lymphocytic lymphoma	B	+	++++	++++	++++
Follicular center cell small cleaved	B	+++	++++	++++	++++
Follicular center cell large cleaved	B	−	++	++	++++
Follicular center cell small noncleaved	B	++++	++	+	++++
Follicular center cell large noncleaved	B	++++	++++	++++	++++
Immunoblastic sarcoma	B	++	++++	++++	++++
Plasmocytoid lymphocytic lymphoma	B	++	++	+	++++
Leukemia reticuloendotheliosis (hairy cell)	B	+	++++	+	+
Small lymphocytic lymphoma	T	+	−	+++	++++
Convoluted T-cell lymphoma	T	+++	+++	++	++++
Immunoblastic sarcoma	T	+	+++	++	++++
Mycosis fungoides and sezary cell lymphoma	T	−	+++	+	++++
Epitheloid cell lymphoma	T	−	+	−	++++
Histiocytic lymphoma	O	+++	++	++	+++
U cell lymphomas	O	++++	++	+	++++

Note. Since most of the above lymphoid malignancies vary from patient to patient, this table represents an average growth in some lymphoid organs (5–7).

in convoluted T-cell lymphoma, thymic and spleen involvement may vary from moderate to gross, lymph node involvement is usually heavy, and, in approximately 30% of the cases, bone marrow infiltration with resultant bone marrow insufficiency occurs. In Hodgkin's lymphoma cervical lymph nodes are usually first involved, in contrast to other types of lymphomas which can originate in any lymph node. In Hodgkin's disease, liver involvement is often extensive; the bone marrow is rarely affected. The spread of non-Hodgkin's lymphoma is different from that of Hodgkin's disease as there is a tendency for hematogeneous and lymphatic dissemination from the beginning and one-third of the patients with non-Hodgkin's lymphomas develop a leukemic transformation early in the disease. In mycosis fungoides and sezary cell lymphoma as well as epithelial cell lymphoma, which all share T-cell markers, skin involvement is common with little liver and bone marrow involvement. In contrast, other T-cell malignancies such as T-cell lymphomas and T-ALL often grow extensively in the bone marrow and liver. These examples serve to illustrate the principle that homing, growth, and specific organ involvement of leukemias and lymphomas may follow the expected pattern based on normal cell homing properties. However, exceptions to this principle are numerous, and metastatic patterns can even change during the evolution of the disease.

Animal Models. Most animal systems have failed to take into account the probable origin of the leukemias or lymphomas and their natural routes of metastatic spread. The best studied murine cell lines derived from leukemias or lymphomas are routinely passaged as ascites tumors following intraperitoneal injection and/or as *in vitro* passaged cell lines. However, we found that two murine leukemia cell lines (L1210 and P388[2]) grew very rapidly in the bone marrow (following intravenous injection) and soon completely replaced the normal bone marrow hematopoietic cells (9) (Table II). In marked contrast,

[2] It is important to note that our P388 line is *not* the macrophage-like P388 line that has been selected from the original P388 lymphoid leukemia line (8).

TABLE II. GROWTH OF VARIOUS MURINE AND GUINEA PIG LEUKEMIA OR LYMPHOMA CELL LINES IN VARIOUS ORGANS FOLLOWING INTRAVENOUS INJECTION

	Ref.	Cell marker	Bone marrow	Spleen	Liver	Lymph node	In muscle around injection site
Mouse line							
L1210 Leukemia	(9)	O	++++	+	++[a]	−	−
P388 Leukemia	(8, 9)	O	++++	+++	++++[a]	+	−
L5178Y Lymphoma	(9)	T	−	−	++++[b]	+++	+++
RI Lymphoma	(9)	T	+	−	++++[b]	+	+++
EL4 Lymphoma	(9)	T	−	−	++++[b]	+	+++
L5178Y 616 Lymphoma	(9)	O	−	−	+++[b]	−	+++
L5178Y 1A1 Lymphoma	(9)	O	−	−	+++[b]	−	+++
BCL_1 Leukemia	(13–15)	B	−	+++	++++[a]	−	NT
CH 1 Lymphoma	(24)	B	−	++++	NT	++++	NT
CH 2 Lymphoma	(24)	B	−	++++	NT	++++	NT
Guinea pig line							
L_2C Leukemia	(23)	B	++++	+++	++[a]	++	NT
KSL Leukemia	(23)	B	+	++++	+++[a]	++++	NT

[a] Infiltrative growth.
[b] Nodular growth.

all five cell lines derived from lymphomas produced no bone marrow growth but formed gross lymphomas, principally in the liver. This difference in metastatic spread could not be accounted for by differential entrapment of the cell lines as approximately the same number of cells initially colonized the liver or bone marrows regardless of their origin (9). Furthermore, direct intra-bone-marrow (IBM) injection (9) of the cell lines further substantiated these findings: the two leukemic lines quickly took over the bone marrows and no solid tumors formed outside the bone marrow; the lymphoma lines did not grow and were quickly eliminated from the bone marrow but did form gross lymphomas in the liver and around the injection site in the muscle near the bones (Table II).

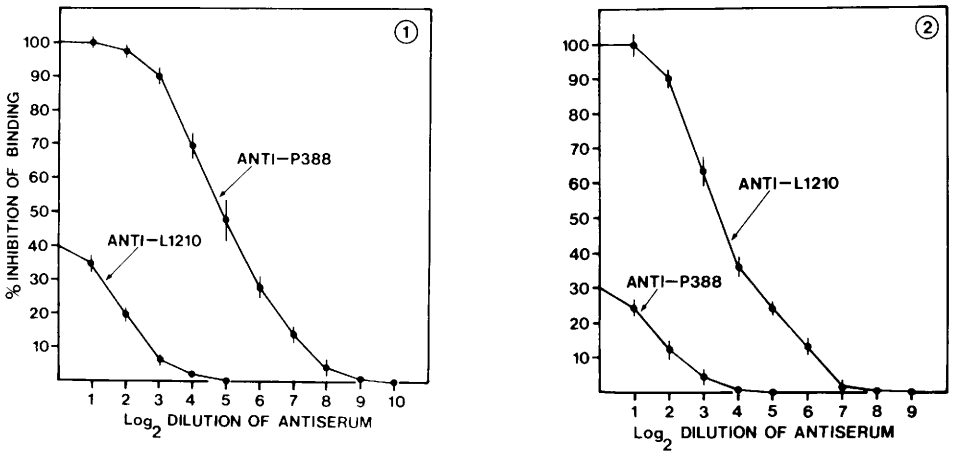
Animal Models for Leukemogenic Metastasis. Based on this work we formulated the working hypothesis that the bone marrow "microenvironment" might in some way aid the growth and/or retention of leukemia, but not lymphoma, cell lines. We then observed that many fluorescently labeled leukemia, but not lymphoma, cells, which were injected intravenously and which homed to bone marrow, were found to exist in "rosettes" or grape-like clusters with a population of unlabeled bone marrow cells (9). Similar grape-like clusters are often observed in bone marrow biopsies of children with ALL and in spontaneous murine leukemias which occurred during the present investigation (our unpublished observations). This phenomenon could be reproduced *in vitro* by incubating labeled leukemia cells with normal bone marrow cells (9). In addition, when leukemia cells were placed in Dexter cultures (10) of adherent "microenvironment cells" from normal bone marrow, they avidly adhered to these cells and rapidly overgrew the cultures (9). Collectively, these data suggest that leukemia, but not lymphoma, cells interact in a novel way with adherent bone marrow cells and that this interaction might be responsible for their retention and rapid proliferation in the bone marrow. We suggest that this phenomenon represents a normal mechanism whereby nonadherent hemopoietic bone marrow cells interact with "microenvironmental" adherent cells as a requirement for stem cell maintenance and differentiation (9, 10).

Our current efforts using this model are aimed at the identification of the putative receptor responsible for the remarkable interaction between the leukemia cells and bone marrow adherent cells. As a first step to attempt to produce a MAb against the putative receptor (see below) we have immunized rats against the two leukemia lines

and have produced antisera which inhibit the adherence and growth of the leukemia cells in Dexter cultures. Interestingly, antisera produced against L1210 cells inhibit L1210 adherence much better than P388 adherence and vice versa (Figs. 1 and 2). This suggests that more than one receptor may be involved in the bone marrow adherence phenomenon.

Most attempts to grow human leukemias in nude mice have failed or have only led to local (subcutaneous) growth of the leukemia cells (11). In contrast, Watanabe and coworkers (12) successfully transplanted the Ichikawa human ALL cell line in nude mice and demonstrated infiltrative spread of the ALL cells in a pattern that closely resembled the spread in ALL patients. Of particular interest is the fact that the bone marrow of these mice was found to be densely packed with ALL cells. This suggests that human leukemia cells might recognize "homing" markers on murine bone marrow cells. Consistent with this interpretation is our finding that human leukemia cells adhere avidly to the murine "Dexter" adherent cells and, vice versa, murine L1210 and P388 leukemia cells adhere avidly to human adherent cells (Figs. 3 and 4).

A spontaneous B-cell leukemia (BCL_1) that arose in a BALB/c mouse (13, 14) has been used as a model for human chronic lymphocytic leukemia (CLL). The tumor causes an enormous splenomegaly and leukemia with little or no lymph node or thoracic duct lymph involvement. The failure of BCL_1 cells to enter the lymph nodes or the thoracic duct lymph may be caused by their inability to penetrate the high postcapillary venules (HEV) of the lymph nodes. This failure might be due to the lack of a cell surface receptor for a determinant on the HEV. Krolick and colleagues (15) considered two possibilities as most likely, (1) BCL_1 cells represent a relatively immature population of B cells that have not yet developed competence to recognize and traverse HEV or (2) BCL_1 cells are representative of a population that would normally recirculate, but have lost this ability due to a membrane defect (loss of HEV receptor?). These authors point out that BCL_1 seems to be more analogous to prolymphocytic leukemia (PL-CLL) than to conventional CLL. The features in common with PL-CLL include leukemia, massive splenomegaly and hepatomegaly, and the absence of lymph node enlargement. In contrast CLL patients usually have massive lymph node enlargement. Another interesting feature of this model is that BCL_1 cells can be induced to differentiate into more mature B cells *in vitro* (15) and possibly *in vivo*. This has also been shown for CLL cells *in vitro* (15).



FIGS. 1 and 2. Rats were immunized ip with 1.5×10^7 P388 or L1210 cells weekly for 3 weeks, rested for a further 3 weeks, injected iv with 1.5×10^7 cells and bled 3 days later. For the inhibition experiments ^{51}Cr-labeled P388 or L1210 cells were incubated at rt with various dilutions of antisera for 20 min, washed, and placed on Dexter culture monolayers. The data are expressed as the percentage inhibition of binding ± SD relative to control cells incubated with normal rat serum.

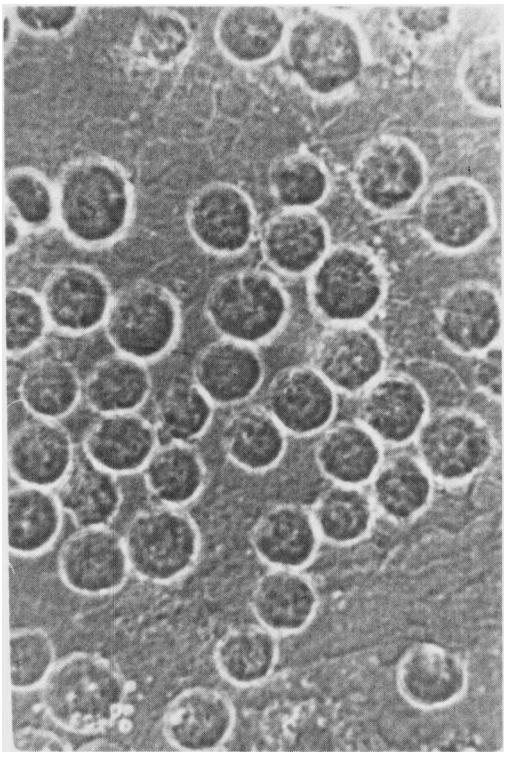


FIG. 3. Adherence of human B-ALL cell lines (RPMI 8392 and CCRF-H-5B2) to a murine bone marrow monolayer. 10^7 leukemia cells were added to a flask containing bone-marrow adherent cell monolayers. After incubation at 37°C for 2 hr the supernatant containing nonadherent cells was removed, the monolayers were vigorously washed and inverted prior to photography (the leukemia cells were actually "hanging" from the inverted monolayer).

Thus, more immature malignant lymphocytes might home to an organ (e.g., spleen) and be induced to differentiate into more mature cells. Each new differentiation state could result in the appearance of new cell surface receptors which might result in new homing patterns and tissue distribution.

Animal Models for OSM of Lymphomas. Nicolson and colleagues (16) have used the murine RAW-117 lymphosarcoma system to study organ specific metastasis. In common with human lymphosarcoma, RAW-117 cells appear to have been derived from the B-cell lineage, and the most commonly colonized organs are liver, spleen, and lymph nodes. Selections for enhanced metastatic lines were made resulting in the RAW-117-H10 cell line which forms several hundred fold more liver foci than the parental RAW-117-P cell line. Recently these workers have shown that liver colonization by RAW-117-H10 cells may be related to the expression of an embryonic murine liver antigen(s) (EML) or its cross-reactive determinants. Pretreatment of H10 cells with $F(ab')_2$ polyclonal antibody fragments against EML resulted in almost complete inhibition of liver metastasis. EML is present on embryonic mouse liver cells but not in embryonic mouse retinal cells and appears to mediate embryonic cell adhesion. These experiments suggest that RAW-117 lymphosarcoma cells express a cell-surface antigen(s) related to an antigen(s) involved in embryonic cell adhesion and that this lymphoma might use this mechanism for liver colonization.

Schirrmacher and colleagues (17) have studied the methylcholanthrene-induced DBA/2 T-cell lymphoma L5178Y/Eb (abbreviated

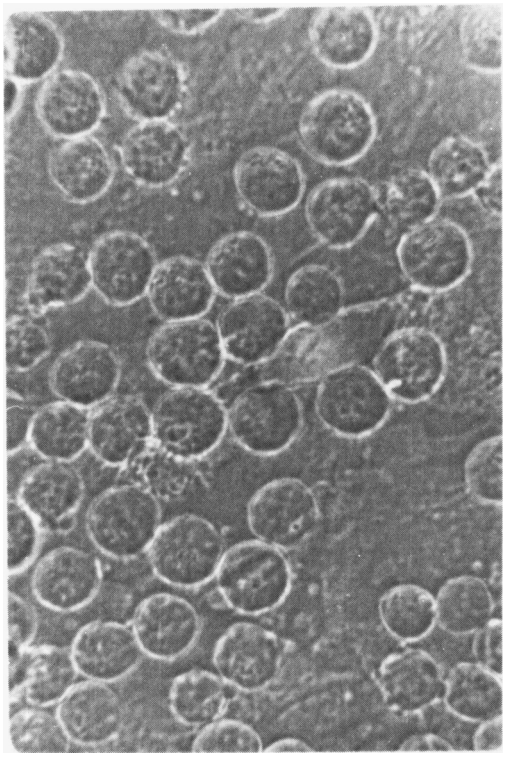


FIG. 4. The same as Fig. 3 except that L1210 murine leukemia cells are adherent to a human bone-marrow monolayer.

Eb) with low metastatic capacity and its spontaneous variant ESb which has high metastatic capacity. These authors suggest that ESb cells, which metastasize to the liver and form rosettes with hepatocytes, do so because the hepatic binding protein recognizes terminal galactose residues which are expressed on ESb, but which are sialylated on Eb cells. In reversal of this, other recent studies demonstrate the existence of receptors on lymphoma cells which appear to recognize specific determinants on endothelial cells. Butcher *et al.* (18) demonstrated that certain murine lymphomas bind specifically to Peyer's patch HEV, some bind almost exclusively to peripheral node HEV, and others demonstrate no detectable HEV binding. Lymphoma cells with no HEV binding capacity grow into local, nonmetastatic lymphomas following subcutaneous inoculation or home to the spleen following intravenous injection. On the other hand HEV-positive lymphoma cell lines metastasize to the appropriate lymph nodes following intravenous injection. Peyer's patch and peripheral node HEV appear to bear distinct determinants for recognition by lymphocyte subpopulations and lymphoma cells. Cells which have restricted specificity would be expected to bear receptors for only one HEV type (18). This model has recently received strong support by Gallatin and coworkers (19) who produced a monoclonal antibody (MAb) specific for a lymphocyte surface molecule that appears to mediate recognition of lymph node HEV and to be required for lymphocyte homing into lymph nodes *in vivo*.

We have employed yet another model for the study of site specific spread of lymphoma cells. Marek's disease (MD) is a naturally occurring herpesvirus-induced T-cell lymphoma of chickens which has pathological and etiological similarities to Burkitt's lymphoma of man. One of the similarities is the high incidence of ovarian and liver metastases. The AL-1 MD-derived cell line also displays this pattern of metastasis. Two metastatic variants were selected from this cell line: AL-2 was selected for liver metastasis and produced several hundred fold more liver foci than AL-3 which was selected for ovary preference. We postulated that a cell surface receptor was involved in determining the specificity of liver metastasis in this system. Thus, we immunized mice with AL-2 cells and successfully generated a MAb which reproducibly and specifically blocked the capacity of AL-2 cells to produce liver foci and metastases (20). These experiments strongly suggest that a receptor-mediated mechanism(s) may be operative in this model.

Previously the presence of subpopulations of lymphocytes with specific receptors for HEV of various lymph nodes had been shown using a frozen section assay (18). We have adapted the assay to our system (Fig. 5) and have found that AL-2 cells adhere much more strongly to liver frozen sections than AL-3 cells but there is no difference in their capacity to bind to frozen sections of other organs (Fig. 6). More important, however, is the observation that virtually all modifications or treatments which were shown to inhibit liver specific metastasis of AL-2 cells *in vivo* also specifically inhibit their capacity to adhere to liver frozen sections. Of particular interest was the finding that L-fucose and L-

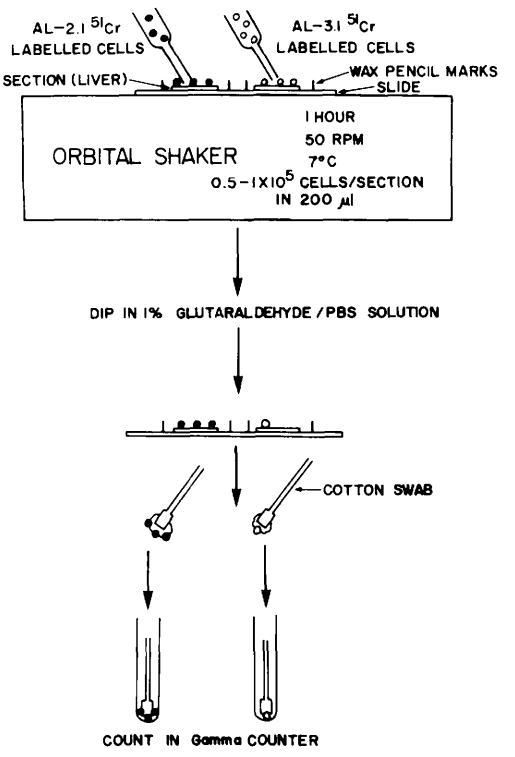


FIG. 5. Schematic representation of *in vitro* frozen section assay.

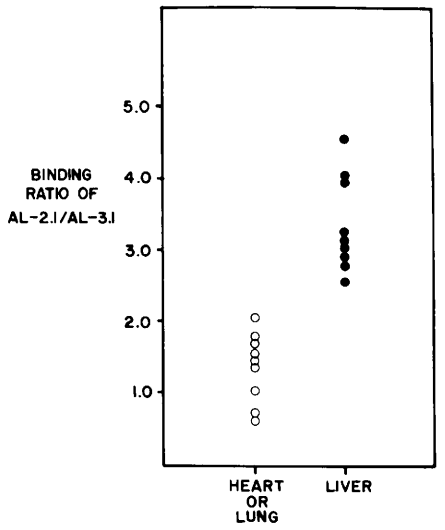


FIG. 6. Ratio of binding of AL-2/AL-3 to different tissues. A total of nine representative experiments performed over a 2-month period is shown.

fucose containing compounds specifically inhibited the capacity of AL-2 cells to form liver foci and adhere to frozen sections of liver. Furthermore, preinjection of lectins which specifically bind to fucose (*Ulex europaeus* and *Lotus tetragonolobus*), but not those which bind other sugars (e.g., *Maclura pomifera,* MPA), inhibited liver foci formation. The fucose binding lectins were found to bind to liver endothelial cells but not to liver parenchymal cells. Finally, pretreatment of frozen sections of liver with fucose binding lectins specifically inhibited AL-2 adherence (Fig. 7).

These experiments suggest the existence of an L-fucose-recognizing lectin-like receptor on AL-2 cells which mediates adherence by recognition of fucose residues on liver endothelial cells.

These results are especially interesting in light of a recent report (21) that L-fucose may be one of the recognition units involved in normal homing of T cells to lymph nodes. Perhaps the best biochemical evidence for the nature of the receptors involved in the normal homing of lymphocytes is that of Gallatin and co-workers (19). These investigators have isolated and purified the molecule that mediates the specific binding between T cells and the HEV of specific lymph nodes to which these cells normally home. This glycoprotein (mol wt = 90,000) may be the normal homolog of the tumor cell receptor or may derive from a family of such molecules. Since lymphocytes appear to have specific homing patterns determined by specific cell surface receptors, it will also be of importance to compare this molecule to those from leukemias and from solid tumors. Do solid tumors and leukemias share similar homing receptors or have they each evolved or modified their own mechanisms of normal (embryonic?) cellular function into one that achieves organ specificity?

Surface lymphoid differentiation markers have been useful for classification of leukemias, perhaps usually indicating the origin of the leukemia (22). However, as discussed above, these markers do not correlate well with the clinical pattern of the disease. We would speculate that the differences in the clinical picture among leukemias bearing the same differentiation markers are at least partially due to the presence of different homing receptors or perhaps due to a different density of expression of the same receptors in some cases.

Conclusions. In the present minireview we have discussed several types of model systems which have given valuable clues to the ways in which leukemia and lymphoma cells mediate organ specific metastasis. Most patent is that these types of malignancies probably utilize *normal* receptor-mediated mechanisms

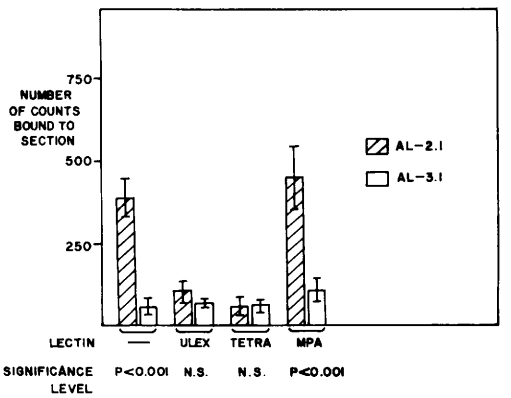


FIG. 7. Inhibition of *in vitro* frozen section adherence assay with various lectins. Frozen sections were incubated with lectins and washed prior to the addition of ^{51}Cr-labeled AL-2 or AL-3 cells.

for organ specific recognition. The animal models which have been most extensively studied indicate that the following three recognition mechanisms can be employed by metastatic lymphoma variants:

(1) Normal organ cells have receptors for determinants on metastatic variants (17);

(2) metastatic variants have receptors for determinants expressed on endothelial cells (2, 19); and

(3) an undefined interaction occurs between normal organ cells and metastatic variants (16).

A great deal of evidence suggests that organ specific metastasis is at least partially mediated through carbohydrate determinants which are recognized by receptors. It is possible that these receptors may be part of a larger family of recognition molecules which mediate normal cell–cell interactions. Despite this, a role for a "microenvironmental" mechanism cannot be ruled out and, indeed, is not mutually exclusive of the receptor-mediated adherence mechanism. In fact, in our bone marrow model our preliminary results suggest the existence of growth factors which are secreted by adherent bone marrow cells and which strongly stimulate the growth of the leukemia cell lines. Nevertheless, the avid binding of leukemia cells to the adherent cells of the bone marrow appears to be an important mechanism whereby leukemia cells are "held" in the bone marrow. The continued development of MAbs which recognize organ specific receptors on tumor cells, the isolation of these receptors, and their molecular biology should reveal whether a multigene family for organ specific recognition exists. These receptors will serve as *functional* markers in contrast to conventional markers such as T- and B-cell determinants. While it is true that T- and B-cell markers may indicate the probable cell lineage of the transformant, they do not, for example, explain why ALL grows in the bone marrow and not in the spleen. We suggest that the identification of "homing" receptors using MAbs will, for the first time, enable us to gauge the status of a malignancy, accurately determine the prognosis, and even allow us to choose the appropriate MAb to be used for the therapy of individual leukemias.

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