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# INSIDE LAB INVEST

***A NOVEL CELL MODEL OF ANAPLASTIC LYMPHOMA:*** Despite major progress in understanding development and pathogenesis of neoplasms, useful animal models are lacking for many of these diseases. One approach is the passage of human lines as xenografts in immunocompromised mice. This stratagem has many advantages, but suffers from difficulties in establishing xenograft lines, from the dysfunction of the hematopoietic system in immune-deficient mice, and from cross-species differences in the activity of cytokines. The latter issues are especially significant for hematopoietic disorders. An alternative approach is to develop mouse lines with phenotypes similar to human diseases. In some cases, gene transfer technology can be used to recapitulate changes that occur during spontaneous carcinogenesis. Anaplastic large cell lymphoma (ALCL) is a T or null cell lymphoma of uncertain specific origin. Because of its heterogeneity, it is possible that this category actually subsumes a collection of related diseases. In this issue, **Bittner et al** (Lab Invest 2000, 80: 1523–1531) describe the properties of a murine cell line derived from a IL-9-dependent T helper clone, TS1, that was rendered IL-9-independent by transfection with an IL-9 cDNA. The resulting line, TS1G6, has morphology, surface markers, and other properties typical of a subset of human ALCL in that it does not express the anaplastic lymphoma kinase. Injection of these cells into immunocompetent syngenic mice induces a disease remarkably similar to human ALCL. In principle, this should be an excellent tool for the development and validation of therapeutics targeted to this aggressive lymphoma.

***ON THE IMPORTANCE OF BEING, OR NOT BEING, CLONAL:*** Adult tissues that regenerate are composed of a quilt of clonal patches, each patch issued from a tissue stem cell that amplifies by symmetrical division and subsequently differentiates. Laser microdissection combined with PCR enables investigators to study the somatic genetics of microscopic structures and lesions in much the same way that immunohistochemistry enabled the mapping of diverse cell populations using immunophenotypes. Because tumors can be regarded as the product of a micro-evolutionary process, it is not surprising that the combination of laser microdissection and PCR is being used to answer questions about the clonal composition of tissues, and the tumors derived therefrom, as illustrated in two papers appearing in this issue of the journal.

Using the HUMARA assay, **Paradis et al** (Lab Invest 2000, 80: 1553–1559) present data indicating that as much as 51% of cirrhotic nodules in livers affected by Hepatitis C are monoclonal. Mono- and polyclonal nodules were randomly distributed throughout the liver, and the size of the monoclonal nodules was significantly larger than the polyclonal ones. Interestingly enough, the group at Bicetre was unable to come up with a set of morphological features that distinguished the two classes of lesions. Only iron overload correlated with monoclonality. Given the fact that most hepatocellular carcinomas arise from the malignant transformation of cirrhotic nodules, it makes sense to think, **Paradis et al** suggest, that the monoclonal population of nodules represents the fertile soil for the emergence of fully malignant lesions. The cirrhotic liver that accumulates monoclonal nodules should theoretically be at higher risk for HCC than the nodular liver mostly composed of polyclonal nodules. Whether this is indeed a practical way to assess the risk of HCC in cirrhotic livers remains to be proven, but it is an interesting and promising first step.

Follicular lymphoma is an indolent neoplasm with a median survival of 8 to 10 years. A number of independent observers have reported the presence of clusters of proliferating monocytoid B cells, and Nathwani has recently presented data suggesting that cases with greater than 5% monocytoid cells had a shorter disease-free and overall survival than pure follicular neoplasms. It was speculated that some of the cases with proliferating monocytoid B cells may be issued from a pluripotent precursor memory B cell that differentiates into multiple cell types. In this issue, **Robetorye et al** (Lab Invest 2000, 80: 1593–1599) investigate the clonal relationship between the follicular and monocytoid B cell components of four cases of nodular lymphoma. Using the rearrangement of the immunoglobulin heavy chain gene, the presence of bcl-2 MBR/JH DNA fusion products, and microdissection, they show clonal identity of the two morphologically distinct cell populations in three out of four cases. Large scale

studies focusing on the question of whether the clonal relationship of the two components is prognostically significant should tell us something about the importance of being clonal!

***CADHERIN IN MAST CELLS:*** In the beginning it seemed simple. Epithelial cells express surface membrane proteins of the cadherin family. These proteins, through their extracellular domains, bind the cadherins on adjacent cells to form tight *adherens* junctions. With the discovery of different types of cadherin, it was realized that a cadherin of one type will preferentially join only with a cadherin of the same type, leading to homotypic junctions and the sorting out of heterogeneous cell populations into homogeneous islands. Mixtures of E-cadherin– and P-cadherin–expressing cells, when propagated in culture, form homogeneous patches of E- or P-cadherin–expressing cells. Thus, cadherins are essential for tissue pattern formation during embyrogenesis and for the integrity of epithelial tissues. With the discovery that a cassette of cytoplasmic proteins, collectively called the catenins, mediate the attachment of cadherins to the cytoskeleton and to other signaling molecules, it was appreciated that the cell could regulate its adhesion (inside-out signaling) by modification of the catenins. These discoveries, together with the recognition of a dual role for beta catenin in mediating not only cadherin-based adhesion but also cell growth via the Wnt-1 signaling pathway (outside-in signaling), have led to an appreciation of cadherin and the catenins as major tumor and metastasis suppressor molecules involved in a variety of processes that control epithelial cell growth and morphogenesis. New observations over the past few years, including the contribution by **Tegoshi and colleagues** in this issue (Lab Invest 2000, 80: 1571–1581), broaden considerably the scope of biologic phenomena that involve cadherin. With the discovery that E-cadherin binds $\alpha^{E}\beta^{7}$ integrin on the surface of intraepithelial lymphocytes, a role for this molecule in mediating heterotrophic interactions between epithelial and nonepithelial cells was established. Other roles for cadherin have emerged in Langerhans dendritic cells, in erythropoietic cells, and possibly in lymphocyte differentiation or lymphocyte homing. Now **Tegoshi et al** extend this understanding by demonstrating a direct role for cadherin/catenin in mast cell differentiation and mast cell adhesion to epithelial cells. In their studies, they demonstrate the highest levels of E-cadherin, catenin, and p120 (another component of the cytoplasmic adhesion complex) in bone marrow-derived mast cells; these levels fall in peripheral blood mast cells, suggesting a role for cadherin in mediating the differentiation of these cells. Correspondingly, suppression of cadherin binding by blocking antibodies or peptides stops the clonal proliferation of mast cells in culture, as well as their adhesion to an epithelial surface. The pathologic significance of these observations remains to be elucidated. However, they provide evidence for a broad and previously unappreciated role for the cadherins and raise the possibility that molecular pathways akin to those guiding embryonic differentiation and tissue patterning might also guide the homing and differentiation of inflammatory cells to sites of inflamed epithelium.