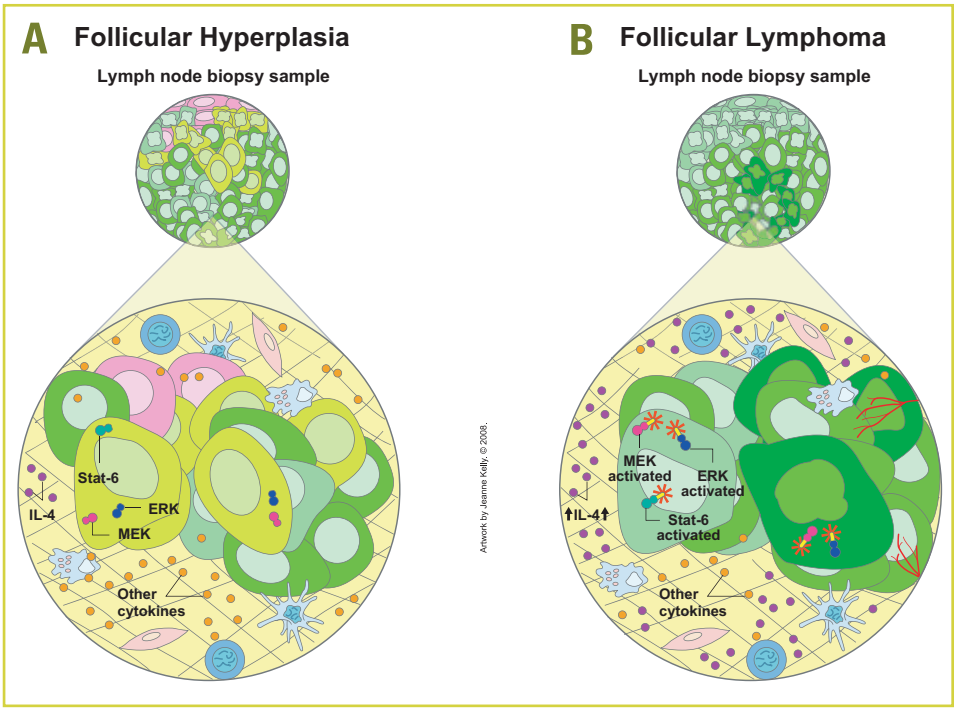
Microenvironment May Drive Follicular Lymphoma

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma and represents 20 percent of all lymphomas diagnosed in adults. Although it is a slow growing cancer, FL is largely incurable — half of all patients diagnosed with the disease die within 7 to 10 years.

There is compelling evidence that the surrounding microenvironment plays an important role in the survival and proliferation of FL. The disease, which develops from immune cells called B cells, is most commonly found in the lymph nodes. Lymph nodes also contain a number of other immune cells, such as T cells, macrophages, and dendritic cells. All of these cells are capable of exerting effects on FL, either through direct cell-cell interaction or by secreting signaling proteins called cytokines.

To learn more about the FL microenvironment, Katherine Calvo, M.D., Ph.D., a Staff Clinician who works in the CCR Laboratory of Pathology with Elaine Jaffe, M.D., took a close look at several proteins known to be important in immune cell signaling. To do this, Calvo and Jaffe collaborated with in-house experts in proteomics, which is the large-scale study of proteins. The study is described in the August 5, 2008, issue of *Blood*.



As shown in the illustration above, a proteomics analysis of the differences between hyperplasia (figure A) and lymphoma (figure B) in follicular lymphoid tissue revealed that while many other cytokines are less active in lymphoma, IL-4 is more active and expressed at much higher levels. The research team also found phosphorylation of the proteins MEK, ERK, and Stat-6 in lymphoma compared to the activity of these proteins in hyperplasia. This outcome occurred despite the fact that overall protein levels were similar in these two types of tissues.

The research team collected protein from lymph node biopsies from 50 FL patients and 23 patients with follicular hyperplasia (an expansion of benign B cells) and measured levels of a number of cytokines. Of the 10 cytokines measured, nine were expressed at lower levels in FL compared to follicular hyperplasia. The authors speculate that this might have occurred because the immune system suppressed cytokine production in an attempt to curb tumor growth. Only one cytokine, IL-4, was expressed at higher levels in FL than in hyperplastic lymph nodes. IL-4 is secreted by immune cells called type 2 helper T cells and regulates proliferation, differentiation, and apoptosis of B cells. Interestingly, gene expression of one of the receptors for IL-4 was previously shown to be up-regulated in FL.

The team used a proteomics technique called reverse-phase protein microarray (RPMA) to profile a number of proteins known to be involved in cytokine signaling. RPMA allows researchers to quantitatively compare proteins among large numbers of samples. In addition to querying protein levels, RPMA can look at whether proteins have been modified; for example, it can determine whether a protein has been phosphorylated, which commonly occurs when signaling proteins are activated. The scan revealed increased phosphorylation of the proteins MEK and ERK in FL compared to follicular hyperplasia, despite the fact that overall protein levels were similar. Although MEK and ERK can be phosphorylated in response to many different cytokines and growth factors, it is possible that their activation in FL is related to the high levels of IL-4. Stat-6, another protein known to be activated in response to IL-4, also demonstrated increased levels of phosphorylation in FL samples.

This study showed that the FL microenvironment is characterized by overall low cytokine levels but high levels of IL-4. Along with evidence that the MEK/ERK pathway and Stat-6 are activated, these findings provide a better understanding of the biology of FL and should help in the development of effective molecularly targeted therapies for this disease.

Reference

Calvo KR, Dabir B, Kovach A, Devor C, Bandle R, Bond A, Shih JH, Jaffe ES. IL-4 protein expression and basal activation of Erk in vivo in follicular lymphoma. Published online in *Blood* August 5, 2008 [Epub ahead of print].