A majority of healthy persons have, in their normal B cells, the defining event of follicular lymphoma — a t(14;18) translocation that brings together BCL2 and the gene encoding the immunoglobulin heavy chain (Fig. 1). The expression of BCL2 (which inhibits apoptosis) is consequently increased and contributes to the transformation of the normal B cell into follicular lymphoma. These events alone are not enough for complete transformation; additional processes are required. A recent report by Roulland et al. describes one such process and indicates that the cells with t(14;18) in healthy persons are closer to follicular lymphoma than was hitherto suspected.

Previously, it was thought that resting, naive, mature B cells in healthy persons had the t(14;18) translocation. Roulland et al., however, showed that these cells have undergone immunoglobulin class-switch recombination, a process that takes place during the germinal-center response to antigenic stimulation. This implies that the t(14;18)-positive cells are not naive but are capable of responding to stimulus by an exogenous antigen such as a virus or perhaps an autoantigen.

How often do normal B cells with t(14;18) undergo transmutation into follicular lymphoma? Pretty rarely, since t(14;18) can be detected in more than 50% of healthy persons, and the incidence of follicular lymphoma is roughly 1 case per 24,000 persons per year in the United States. A clone of t(14;18)-positive normal B cells can, however, persist for at least 3 years in healthy persons. In rare cases, persons have a pronounced peripheral-blood B lymphocytosis (an abnormal increase in the number of lymphocytes, which can be caused by viral infection), often in association with t(14;18). A type of follicular lymphoma has been described in which t(14;18)-positive cells expressing BCL2 are observed in histologically abnormal follicles present in lymph-node biopsy specimens from persons without overt disease. In some of these persons, frank follicular lymphoma develops within a few years, but in others, the process can remain benign for more than a decade. It seems likely that each of these clinical conditions represents a different stage in the molecular and cellular pathogenesis leading to follicular lymphoma.

There is also marked heterogeneity in overt follicular lymphoma. Gene-expression profiling has shown a distinct pattern of gene expression associated with an indolent form of the disease, which is present in about three quarters of patients (with a median survival of 11.1 years), as compared with the pattern associated with aggressive disease (median survival, 3.9 years). The most important difference in gene-expression profiles points to the nature of the infiltrating immune cells. Thus, the immune response may regulate the pace of the malignant process in follicular lymphoma and may restrain the proliferation of t(14;18)-positive B cells in healthy persons.

The findings of Roulland et al. also point to a critical influence of the immune response, with emphasis on the t(14;18)-containing B cell itself. The investigators observed that these cells express surface IgD molecules and proposed that they are functional receptors affecting transformation. The surface IgD in these cells must be derived from the IgD gene on the nontranslocated chromosome, since the t(14;18) translocation disrupts the variable regions of the immunoglobulin. The authors observed that the IgM–IgD region was often deleted from the translocation-bearing chromosome (presumably through immunoglobulin class-switch recombination) and was not deleted from the nontranslocated chromosome — suggesting that cells with an intact IgM–IgD region have a survival advantage. Similarly, most follicular lymphomas maintain surface IgM. The authors therefore surmised that stimulation of t(14;18) B cells through their surface immunoglobulin receptors may contribute to malignant transformation (Fig. 1).

Indeed, a study of patients infected with hep-
Hepatitis C virus showed that successful antiviral treatment also eliminated their t(14;18)-positive B cells. Some patients subsequently had a relapse of hepatitis C viremia, and the t(14;18)-positive B cells returned, suggesting that these B cells were responding directly or indirectly to the virus. Given that the surface immunoglobulin receptor is retained in patients with follicular lymphoma, it is tempting to speculate that small-molecule inhibitors of signaling by the B-cell receptor might be effective in treating this disease, should they be developed.

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Figure 1. A New Take on Follicular Lymphoma.
The t(14;18) translocation is likely to occur in a naive B cell. A recent study by Roulland et al. suggests that this B cell, if stimulated by an exogenous antigen such as a virus or autoantigen, may enter into a germinal-center reaction. There, on stimulation by an antigen on the surface of a follicular dendritic cell (FDC), together with a T cell, it may differentiate into a memory B cell, which can still be stimulated by antigen. This type of cell represents the majority of the t(14;18)-positive cells in the blood of normal persons. One of these cells may sustain further oncogenic lesions, leading to full transformation to follicular lymphoma, which may retain dependence on antigenic stimulation.

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