Commentary

Unraveling the Mystery of the Lymphoid Follicle

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The lymphoid follicle is an intriguing structure and yet it is not a structure that has received much attention from pathologists. The intrigue of the lymphoid follicle stems from the complexity of its microenvironment, comprising immune cells, adhesion molecules, cytokines and antigen-antibody complexes, and the relationships between these components in the production of antigen with high affinity and the generation of memory B cells. For the hematopathologist, the lymphoid follicle is intriguing because of the apparent and yet elusive relationship between the secondary lymphoid follicle and follicular lymphoid neoplasms, the main examples being follicular lymphoma, nodular lymphocyte-predominant Hodgkin's disease, and nodular sclerosing Hodgkin's disease. The likeness between the reactive lymphoid follicle and the follicles of these neoplasms is so impressive that one cannot dismiss it as coincidental and is compelled to ask about the relationship between reactive follicular hyperplasia and follicular lymphoid neoplasms.

A significant body of work has provided our current understanding of the structure and function of the lymphoid follicle, and excellent reviews summarizing much of this information have been written.¹⁻³ In particular, Tew and colleagues have reported extensively on the mechanisms involved in the antigen transport pathway that leads to the germinal center reaction.^{1,2,4,5} This pathway is an alternative to trapping and processing of antigen by macrophages and has been termed the alternative antigen pathway. Briefly, antigen-antibody complexes are found within sinusoidal macrophages and on the surface of sinusoidal dendritic cells soon after introduction of antigen. Antigen is delivered to the follicular dendritic cells by movement of either antigen or sinusoidal dendritic cells to the follicular center. By day 3 after introduction of antigen, antigen is found on the surface of follicular dendritic cells as immune complex-coated bodies, also called icosomes. Antigen is then released by follicular dendritic cells and taken up by the B cells of the follicle where it is found in lysosome-like vesicles by day 5. The antigen is processed by B cells (as demonstrated by horseradish peroxidase studies in which the HRP product is found associated with the golgi apparatus) and is transferred to their cytoplasmic surface. B cells present

antigen to T cells and, by the mediation of various cytokines, including interleukin (IL)-2, IL-4, IL-5, IL-6, and interferon- γ , the activation, proliferation, and differentiation of B lymphocytes occur. The end result is the production of memory B cells and antibody-producing cells in response to specific antigen. The follicular dendritic cells play an integral role in the germinal center reaction, and a recent report has shown that follicular dendritic cells can be derived from progenitor cells present in primary lymphoid tissues.⁶

The lymphoid follicle has been all but overlooked by pathologists, perhaps because it is so commonly viewed at the microscope. Much of the focus on reactive follicular hyperplasia (RFH) by surgical pathologists revolves around its distinction from follicular lymphoma (FL). The first-year resident in surgical pathology can recite the litany of morphological criteria that distinguish RFH from FL. The features of RFH include an intact lymph node architecture, follicles of varying sizes and shapes, distinct and often well developed mantle zones, polarization of the germinal center, an admixture of lymphoid cell types, and tingible body macrophages. In contradistinction, she learns that FL is characterized by an effaced lymph node architecture replaced by relatively uniform lymphoid follicles, often arranged in a back-to-back pattern, attenuated or absent mantle zones, lack of germinal center polarization, and absence of tingible body macrophages. The only similarity that might receive mention is that both lesions represent nodular proliferations of lymphocytes.

When this first-year resident becomes an immunopathology fellow, she learns that the immunophenotypic similarities between FL and RFH are remarkable, even though the underlying natures of the lesions are different. Both FL and RFH represent nodular proliferations of B lymphocytes that are centered around a highly organized structure of immune cells. Both FL and RFH are supported by a complex three-dimensional network of antigen-presenting cells, the follicular dendritic cells, that provide a framework through their dendritic processes and are integral to the function of the lymphoid follicle. Within and around the lymphoid follicles are large num-

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bers of T lymphocytes that may represent a significant percentage of the constituent cells in the lymph node. The majority of these are CD4+ T cells, a subset of which express CD57. In both RFH and FL, the interaction between B lymphocytes and follicular dendritic cells is mediated by intercellular adhesion molecule 1/vascular cell adhesion molecule 1 on the FDCs and lymphocyte function-associated antigen 1/very late antigen 4 on B lymphocytes.^{7,8} However, the immunoarchitecture of RFH and FL is not identical, as FL typically shows considerable numbers of B cells (neoplastic B cells) in the inter-follicular regions and the B lymphocytes in FL overexpress BCL-2 oncoprotein, features not seen in RFH.

At a molecular level, the distinction between RFH and FL is apparent, although, interestingly enough, some similarities still exist. It is now well known that follicular lymphoma represents a clonal B cell neoplasm characterized by the translocation t(14;18), which results in the overexpression of the oncoprotein BCL-2, a high level of which protects the cell against programmed cell death or apoptosis. The neoplastic cells of FL undergo somatic mutation at a high rate, a mechanism similar to that which occurs in the reactive lymphoid follicle during the production of memory B cells. It is of interest that recent studies of Hodgkin's disease show that in at least a subset of cases, Hodgkin's cells represent B cells with features of germinal center derivation, including the propensity to undergo somatic mutations,⁹⁻¹¹ and that there exists a close relationship between Hodgkin's cells and follicular dendritic cells.^{12,13}

In this issue of the *Journal*, Tsunoda and colleagues provide more information on the lymphoid follicle in their report on the expression of Ca²⁺-binding proteins in RFH and in FL.¹⁴ Their study shows extensive Ca²⁺ capture in follicular dendritic cells but not in the lymphocytes of the lymphoid follicle. As one might expect, at least some similarities between RFH and FL were identified in the distribution of Ca²⁺-binding proteins. Furthermore, their study suggests that the Ca²⁺-binding proteins on follicular dendritic cells of grade I follicular lymphoma may resemble those of the germinal center light zone, whereas Ca²⁺-binding proteins on follicular dendritic cells of grade III follicular lymphoma may resemble those of the germinal center dark zone.

Although the relationship between reactive follicular hyperplasia and follicular lymphoma has been an elusive one, studies such as that of Tsunoda et al are making inroads into our understanding of this relationship. The current body of evidence suggests that the neoplastic B cell population in follicular lymphoma uses and, in fact appears to be dependent on, the highly organized micro-

environment of the lymphoid follicle for its maintenance and growth. This apparent reliance of the neoplastic B-cells of follicular lymphoma on the immune system's complex machinery adds intrigue to the story of follicular lymphoma. And there's nothing like a good story.

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