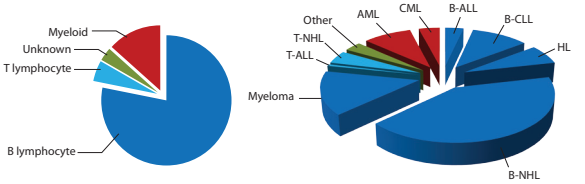
The Normal Process Of B Cell Differentiation Makes Them Susceptible To Mutations That Can Lead To Cancer

by Steve Anderson, Ph.D.

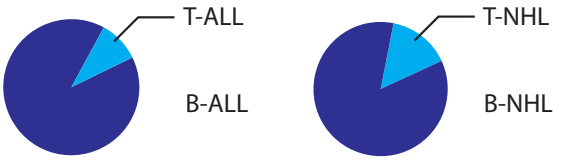
One interesting observation that I made from looking at the frequency or incidence of the different types of leukemias and lymphomas is that the great majority of them come from cells of the B lymphocyte lineage. Since this was somewhat of a surprise to me, I wanted to explore this further. I suspected it was due to the mechanisms of gene rearrangement and mutations that are an integral part of the mechanism by which B cells generate antibodies and respond to stimulation by antigens. After some additional research I believe these are the primary mechanisms that make B cells susceptible to becoming cancer cells. However, there are other mechanisms that also come into play. Although similar mechanisms are used by T cells to generate their antigen-binding receptors, these mechanisms are more prevalent and more extensive in B cells than in T cells.

How B Cells Get Into Trouble While Making Antibodies

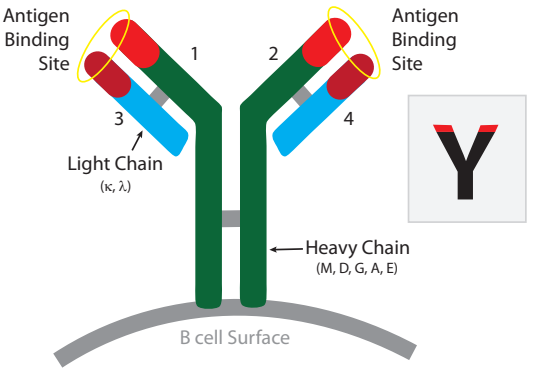
B cells ultimately develop into plasma cells which are the cells of your immune system that make antibodies. Using a variety of specialized genetic mechanisms B cells are able to produce antibodies that recognize virtually any foreign substance or entity you could ever come in contact with. Class Switch Recombination (CSR), Somatic Hypermutation (SHM), and Affinity Maturation are genetic mechanisms that are unique to B cells. It is these specialized genetic mechanisms that can get the B cells into trouble because they work by creating rearrangements and mutations in the B cell's DNA—on purpose. This is how the incredible diversity in antibodies that we need to survive is generated. As a result of DNA rearrangements, that is DNA strand breaking and rejoining, translocations can occur. A translocation is when a segment of DNA is joined to another segment of DNA that is far away, or even on another chromosome. Such translocations can



The majority of leukemias and lymphomas are derived from B cells. B-ALL, B-CLL, Hodgkin's Lymphoma (HL), the majority of non-Hodgkin's Lymphomas (NHL) including DLBCL, FL, Burkitt's Lymphoma, and many others, and plasma cell malignancies such as multiple myeloma, are all thought to be derived from B cells.



The majority of Acute Lymphocytic Leukemias and Non-Hodgkin's Lymphoma are of the B cell lineage.



An antibody is a protein molecule consisting of 4 chains, 2 identical large, or heavy, chains, and two identical small, or light, chains. When the antibody molecule is fully assembled it looks kind of like a "Y". (Inset) Each arm of the "Y" contains a site for binding to an antigen (***red***). Another name for antibody is "immunoglobulin", abbreviated "Ig". There are several different kinds of antibodies based on the kind or class of heavy chain they have: IgM, IgD, IgG, IgA, and IgE. There are two kinds of light chain, kappa and lambda. Each individual antibody will have only one class of heavy chain and one type of light chain. However, after stimulation by antigen B cells can switch from one class of heavy chain to another by a process called Class Switch Recombination (CSR). In order to recognize and respond to antigens, B cells display antibodies on their outer surface. When a B cell becomes a plasma cell it will make a similar antibody to the one it had on its surface. The antibodies made by a single B cell or plasma cell are all identical, so each B cell, and each antibody molecule, only recognizes one antigen.

cause genes to be expressed at the wrong times or in a way that they can no longer be turned on and off appropriately. If one or more of these genes is involved in cell division and proliferation, cancer can result.

B Cells Are Susceptible To Genetic Mutations At Two Stages

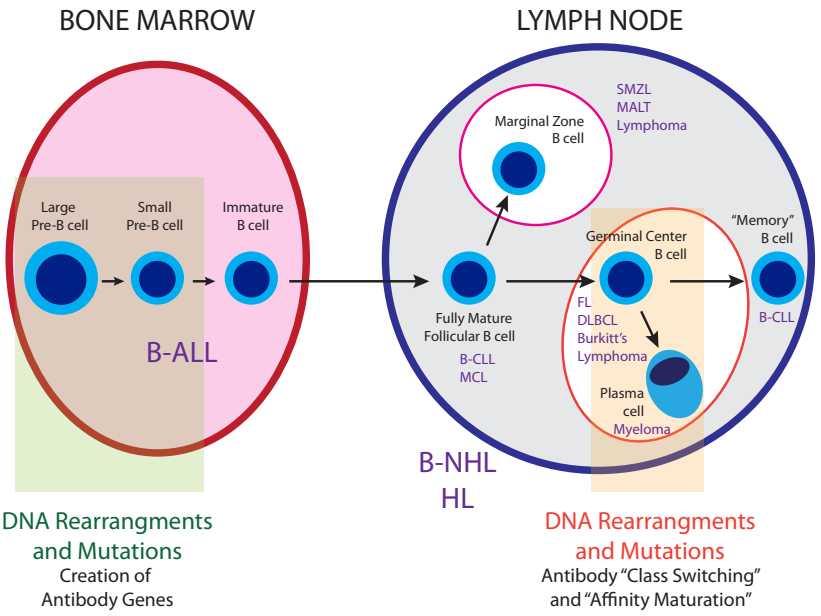
DNA rearrangements and mutation mechanisms are active at two stages during the normal life cycle of B cells, when DNA replication, cells division, and proliferation are occurring. The first is during the early stages of B cell development when Ig genes are first being expressed. Genetic mistakes at this stage can result in B-ALL. The second occurs following antigen stimulation of B cells in germinal centers. Here B cells switch heavy chain classes and actively mutate their Ig genes to create antibodies with greater affinity (stronger binding) to the target antigen. Mistakes at this stage can lead to Hodgkin's Lymphoma and various forms of non-Hodgkin's Lymphoma. (See figure.)

Other Mechanisms

In addition, there are other mechanisms involved in B cell development and differentiation that can result in, or contribute to, the development of B cell cancers. These mechanisms control B cell division and proliferation (expansion), the B cell's life span, and terminal differentiation. These mechanisms also involve signals transmitted to the B cell from the outside through the antibody molecules that are bound to its outer surface. These latter mechanisms most likely contribute significantly to the development of B-CLL and plasma cell malignancies such as Multiple Myeloma since the rearrangement and mutation mechanisms are not active in these cells. ■

Abbreviations & Definitions

B-ALL, B cell Acute Lymphocytic Leukemia; **T-ALL**, T cell Acute Lymphocytic Leukemia; **HL**, Hodgkin's Lymphoma; **B-NHL**, B cell Non-Hodgkin's Lymphoma; **T-NHL**, T cell Non-Hodgkin's Lymphoma; **AML**, Acute Myelogenous Leukemia; **CML**, Chronic Myelogenous Leukemia; **SMZL**, Splenic Marginal Zone Lymphoma; **MALT Lymphoma**, Mucosa-Associated Lymphoid Tissue Lymphoma; **B-CLL**, B cell Chronic Lymphocytic Leukemia; **MCL**, Mantle Cell Lymphoma; **FL**, Follicular Lymphoma; **DLBCL**, Diffuse Large B Cell Lymphoma; **Burkitt's Lymphoma**, a form of B-NHL; **Memory B cell**, a mature B cell that has been through antigen stimulation and produces a highly specific form of antibody to the antigen; **Plasma Cell**, antibody-secreting cell, the final stage of B cell differentiation; **Myeloma**, a cancer originating in plamsa cells.



DNA rearrangements and mutations occur at two different stages during B cell development. The first is during early B cell differentiation in the bone marrow at the pre-B cell stages. The second is following antigen stimulation in the lymph node germinal centers. During these two stages B cells are particularly susceptible to transforming into cancer cells. Other factors can also contribute to cell cancer formation.

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