Pathogenetic Mechanisms in B-Cell Non-Hodgkin’s Lymphomas in Humans

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Abstract

A very large proportion of non-Hodgkin’s lymphoma in the United States are of B-cell origin. This group of tumors includes a variety of different pathological and clinical types. Chromosomal rearrangements play an important role in the pathogenesis of many of these tumors. In B-cells these translocation processes appear to develop as illegitimate products of physiological V-(D)-J or heavy chain switch rearrangements. The biology of the well-known chromosomal translocations is discussed. Additional biological factors in lymphomagenesis (aging, immunodeficiency, role of antigenic stimulation, and genetically determined susceptibility) are discussed.

Introduction

This paper is an introduction to the discussion of the biology of NHLs and will attempt to outline some of the important issues. The NHL group of tumors includes a heterogeneous group of morphological and physiological entities (1, 2). Two different cell lineages, T- and B-lymphocytic forms, are included in most listings. Although T- and B-lymphocytes are derived from the same stem cells, they develop differently and have different functions in immune responses and probably should be considered separately in epidemiological studies. The B-NHLs comprise over 80% of NHLs in the United States (3) and furthermore are the predominant type of NHL associated with the increased incidence of NHLs that has occurred in the last few decades in the United States. Epidemiologists usually consider other lineage-related B-cell tumors such as the B-cell leukemias and Ig-secreting plasma cell tumors separately from the B-NHLs, even though tumors such as chronic B-cell leukemias and multiple myeloma are closely related biologically. One basis for this distinction is that the incidence of B-NHL appears to change in different populations independently of other B-cell tumors (4, 5).

The increased incidence of B-NHLs and multiple myeloma over the last few decades coupled with the number of other varieties of B-cell tumors provides strong evidence that the cells of the B-cell lineage comprise one of the more vulnerable target tissues in the human body for neoplastic development. The increased incidence of B-NHLs appears to affect many if not all of the entities in the Working Formulation (1). There were some indications of specificity. Devesa and Fears (4) noted a decline in low-grade follicular small cleaved cell and intermediate-grade diffuse small cleaved cell lymphomas. The intermediate-grade diffuse large cell lymphoma increased the most dramatically (4). Interestingly, these tumors formed a prominent group in persons exposed to herbicides (6). Diffuse large cell lymphomas are heterogeneous by immunophenotyping, and there is little cytogenetic or molecular information available on these tumors. Since these may represent a chemically induced B-NHL it will be of interest to obtain new information on this type of B-NHL. An increased incidence of high-grade blastic lymphomas associated with HIV infection will also change the distribution of lymphoma types in the near future.

B-Cell Non-Hodgkin’s Lymphomas

The cells of B-NHLs are lymphoblasts or lymphocytes with different morphologies that characteristically express membrane-associated Ig molecules which function as antigen receptors (3). Some may secrete Ig, but for the most part the cells do not acquire an extensive rough endoplasmic reticulum, and Ig secretion, when observed, is usually limited. B-NHL cells are related to B-cells that have completed V-(D)-J Ig-gene rearrangements in the bone marrow but which have not matured into Ig-secreting plasma cells.

The B-NHLs are distinguished biologically from other B-cell tumors by their proclivity for proliferating in secondary lymphoid organs, i.e., lymph nodes, spleen, and mucosa-associated lymphoid tissue and less well understood extranodal sites. Lymphoma cells can also be found in the peripheral blood (7) and secondarily in the bone marrow. Although some lymphomas may have an apparent focal origin in lymph nodes or in extranodal sites, others involve multiple nodes at the time of discovery. This is probably due to the spread of lymphoma cells through the circulation and preferential homing into other lymphoid tissues, characteristics not unexpected from the normal recirculation of B-lymphocytes.

In the discussion to follow on pathogenesis the B-NHLs are divided into two biological groups (Table 1). Group I consists of lymphomas that retain some of the special differentiation phenotypes of B-cells: somatic hypermutation; heavy chain switching; continuous circulation and recirculation; localization to specific regions in lymphoid tissue; the formation of follicle-like structures; and the tendency to have many cells in the tumor in the G0 stage of the cell cycle. These lymphomas are in general the more chronic low- and intermediate-grade tumors in the current classifications. B-cell chronic lymphocytic leukemia should be included in this group because of the many close biological relationships with certain B-NHLs, but it is nonetheless reported as a separate epidemiological entity. Group II lymphomas can appear in any age group but most commonly become manifest in later life. Group II lymphomas are the high-grade blastic tumors that often grow explosively. These tumors are more common in younger age groups. Some of these tumors may be polyclonal. The pathogenetic mechanisms to be described have been developed for some but by no means all of the B-NHLs. The grouping of B-NHLs used here is very oversimplified for purposes of discussion and is not intended to be another classification.

Pathogenetic Factors Relevant to the Epidemiological Problem of Increased Incidence of B-NHL

Chromosomal Rearrangements. Illegitimate chromosomal rearrangement is an important mutational mechanism in many B-NHLs. Understanding the underlying mechanisms that contribute to this process is relevant to the current epidemiological discussion. Little is known about agents that influence abnormal chromosomal rearrangements, but at this meeting Kirsch...
has provided evidence that occupational exposures to pesticides can increase the rate of formation of illegitimate recombinations [e.g., inv (7)pl3;q35] between T-cell receptor genes. While this inversion is not associated with the activation of an oncogene, it suggests that exogenous factors can affect recombinational processes in cells. Garry et al. (8) have described t(8;14) which provides evidence that occupational exposures to pesticides open up a new line of investigation applicable to the biochemical basis for their formation. This would appear to provide an important avenue for epidemiological investigation, i.e., to identify agents in the environment that increase illegitimate exchanges, particularly in B-cells.

The Ig genes in B-cells (and T-cell reactivity genes in T-cells) undergo extensive structural changes during normal development. There are two separate rearrangement processes: V-(D)-J rearrangements that occur during the early pro-B/pre-B stages and heavy chain isotype switching that takes place in mature peripheral B-cells. In each process DNA is broken and rejoined; different enzymes are probably involved in the two processes. The V-(D)-J gene rearranging steps involve Ig genes in three different chromosomal loci: DH—JH, VH—DJH on chromosome (chr) 14; VK—JK on chromosome 2; and Vλ—Jλ on chromosome 22. In all three of these rearrangements distant cis Ig gene elements are brought together or aligned prior to the scission and ligation. The complexities of the cellular steps associated with these rearrangements have been recently reviewed (9). The important end result of gene rearrangement is the formation of a vast number of exquisitely specialized clonotypes, each of which is limited to making only a single type of Ig molecule.

Ig heavy chain switching is a more general process and probably occurs whenever B-blasts are activated into the cell cycle by antigen or nonspecific polyclonal activators such as lipopolysaccharide (see Ref. 10). Switching takes place in several different sites (primary lymphoid follicles, T-rich zones) in the spleen, lymph nodes, and mucosa-associated lymphoid tissue (11). Cytokines such as IL-4, IL-5, γ-interferon, and transforming growth factor β trigger through signal transduction pathways nuclear factors that act on specific DNA switch regions, causing them to assume an open configuration that is a prerequisite for recombination (see Ref. 10).

The V-(D)-J rearrangements and heavy chain switching play an important role in B-cell lymphomagenesis because during these processes Ig genes are opened up and the double-stranded DNA is broken and rejoined. This makes open ends of Ig DNA available not only for the normal rejoicing process but also for illegitimate exchanges. The activity of recombinational machinery is restricted to specific stages of B-cell development (12), and this makes it possible to associate translocations involving: (a) a JH gene with the pro-B period and DH—JH joining; (b) Jκ and Jλ genes with the pre-B period; and (c) switch regions with antigen-activated stages. These associations establish the B-specificity of translocations. The t(14;18)q32q21 which activates bcl-2 and t(8;14)q24;q32 which activates c-myc are the most common reciprocal translocations in B-NHLs. There are other less common but recurring 14q32-associated translocations: (a) t(11;14)q13;q32, in which bcl-1 (13, 14) is activated; (b) t(10;14)q24;q32, in which lyt10 is the target gene (15); and (c) t(14;19)q32q23, in which bcl-3 is the target gene (16).

One putative mechanism for double-stranded DNA breaks in the Ig chromosomal partner is attributed to physiological recombinases. An alternative is that the breaks in the Ig chromosome are caused by other agents that nonspecifically cut the accessible DNA. The cause of the breaks in the non-Ig chromosomal partner is not established. The explanations offered are somewhat controversial. One school of thinking proposes that these are generated by the recombinases themselves that mistakenly recognize signal-like sequences (17) or sequences...
that are “tantalizingly like switch recombination sites” (18) in the target gene. Tycko and Sklar (19) have recently reviewed all of these examples and found that the ectopic recombination signals were highly variable and that many were not close matches for heptamer-spacer-nonamer signals. They concluded that the recombinases may generate breaks in the Ig gene-bearing chromosome but that the breakage events in the target genes were random and probably not site specific. Evidence from molecular analysis of reciprocal break points has shown that the non-Ig breaks are staggered scissions occurring in both strands (18, 20) raising the possibility that other factors such as those triggered by oxidative damage (21) might contribute to chromosomal breakage in both the Ig and non-Ig chromosomes.

Why certain non-Ig genes are selected as “illegitimate” partners in translocations with Ig genes is not yet understood. There may be several contributing factors. First the target (non-Ig) gene may be coincidentally transcribed or synthesized during the Ig gene rearrangement process. Second, the expression of that target gene provides a survival advantage for the B-cell in which it occurs. It seems clear that the non-Ig target gene must be in close proximity to the rearranging Ig gene complex to permit recombination. One mechanism for bringing together genes on different chromosomes is that during DNA synthesis, replication units including polymerases are fixed on the nuclear scaffold. Such complexes form sites where from 300 to 1000 replication forks are located in one unit (22). If loops of chromatin from different chromosomes occupy one of these sites the chromatin could be positioned for recombination during DNA synthesis or transcription.

Illegitimate recombination usually disrupt regulatory sequences of the non-Ig gene, resulting in activations and deregulation of the transcription or translation of the gene. It has been speculated that dysregulation of target genes might provide survival advantage to the cell. If this is so, evidence of clonal expansion of the mutant clone should occur. The phenomenon of clonal stem cell expansion has been observed for the bcr-abl-associated t(9;22) [Philadelphia] translocations in chronic myelogenous leukemia and some B-cell acute lymphocytic leukemias (23). In a mature B-cell it may be more difficult for a clone to expand in the periphery and displace other clones. A brief discussion of two common kinds of translocations in B-cell lymphomas, the t(14;18) that activates bcl-2 in follicular lymphomas and the Myc-associated chromosomal rearrangements (MACTRs) that result in c-myc, provide further insights into this process.

In t(14;18) a break site in JH on chromosome 14 is joined to bcl-2 on chromosome 18 (20, 24, 25). The involvement of the JH breaksite in t(14;18) has suggested that the translocation takes place in the pro-B period of B-cell development when DH rearranges to JH and the JH region is accessible. During this period the Ig gene-specific recombinases (12) as well as terminal deoxynucleotransferase are active. The breaks occur in the 5' end of the JH region, which suggests a potential role for immunoglobulin rearranging recombinases in this step (19). However, the detailed molecular analysis of the break sites has revealed staggered double-stranded breaks in chromosome 18 in some tumors (20), while in others sequences resembling heptamer-nonamer have been described near the break sites (17). There is disagreement on whether the heptamer-nonamer-like signal sequences in the bcl-2 gene are able to signal the recombinases (19). It is possible the break in chromosome 18 may be induced, by DNA-damaging agents rather than by physiological recombinases.

The t(14;18)-carrying cell overexpresses bcl-2 protein (23, 26–28) from its putative time of inception in the pro-B period. Since a major physiological effect of bcl-2 overexpression is to prevent apoptosis and prolong the life of a cell (29, 30), clonal cells carrying this mutation may be able to expand in the pre-B period or even later; however, the abnormal proliferative phenotype is not expressed until the cell becomes a mature B-cell.

Several pieces of evidence suggest that the t(14;18) translocation does not render the cell tumorigenic. First, Limpens et al. (31) have detected t(14;18) translocations in nonneoplastic human tonsil tissues. Second, in a remarkably high number of cases studied (7 of 44), evidence of two different (t(14;18))s has been found in the same case (32). This implies that the t(14;18) may occur far more frequently than the incidence of lymphomas reflects. An implication of these findings is that t(14;18)-carrying cells are generated in many persons in the course of a lifetime, but the cells are either eliminated or never progress to become tumors. This important possibility must await further confirmation. The persistence of cells bearing the t(14;18) translocation during the remission of follicular lymphoma (33) also raises the possibility that these t(14;18)-bearing cells are not part of the tumor population but are precursors from which the tumor was derived. Possibly, then, certain factors or environmental conditions could favor the survival of t(14;18) cells and stimulate the progression toward greater proliferative autonomy.

The bcl-2 gene codes for a Mr 25,000 protein that surprisingly is located on the inner surface of mitochondrial membranes (23). The biochemical mode of action of the gene product is not known, but excessive production of bcl-2 product blocks apoptosis and extends the life of the B-cell (24). The best documented example of apoptosis in B-cells occurs in secondary follicles (34, 35). As centroblasts emerge from these rapid divisions they reexpress Ig molecules that function as antigen receptors. They are then exposed to antigen that has been released from follicular dendritic cells. Those cells that fail to bind to their respective antigen undergo programmed cell death (apoptosis) (34, 35). Centrocyes that do bind antigen can either go on to become Ig-secreting cells (plasmablasts) or memory cells. Survival is influenced by the availability of soluble Mr 25,000 CD23 (released from follicular dendritic cells) and IL-1a, which promote differentiation to plasma cells, or the CD40 ligand that promotes differentiation into memory B-lymphocytes (35). Cells which express large amounts of bcl-2 product would be able to remain viable even though they do not respond to antigen. Hypothetically this could result in salvaging centrocytes that have not been selected by antigen (including centrocytes that could react with self-antigens). These cells stimulated by other factors might then proliferate.

Transgenic strains of mice have been constructed that carry bcl-2 (36–38) under the control of unnatural regulatory influences such as the Ig heavy chain enhancer (Eu-bcl-2) (49) or the bcl-2-Ig fusion gene (38). These mice make it possible to observe the pathophysiological effects of overexpression of bcl-2.

Overexpression of bcl-2 in the B-cell lineage produces several striking immunological effects (30, 36, 38, 39). First there was a 3- to 4-fold expansion of small resting (µ+ d+, CD5~, potential lipopolysaccharide responsive) B-cells in the spleen lymph nodes and bone marrow. Secondary immune responses in the Eu-bcl-2 transgenic mice are also greatly exaggerated and prolonged for many days (36). In the bcl-2-Ig transgenics both
memory B-cells and Ig-secreting cell compartments are expanded; and memory B-cells which usually have a short duration in normal individuals persist for long periods in these transgenics (38). Pathologically enforced bcl-2 expression in Eμ-bcl-2 transgenic mice can induce autoimmune disease (36); furthermore, a few of these mice after long latent periods develop plasmacytomas (40). After a long latent period mice carrying the bcl-2-Ig transgene develop diffuse large cell immunoblastic lymphomas; a number of these have a rearrangement of c-myc (39).

The chromosomal translocations that activate c-myc (MAC-Ts) are t(8;14)q24;q32, t(2;8)q12;q24, and t(8;22)q24;q11. MAC-Ts are found in nearly 100% of endemic and sporadic forms of Burkitt lymphomas, in a high percentage of acquired immunodeficiency syndrome-associated lymphomas (41), and in other lymphomas arising in immunocompromised individuals (42). In many of these conditions the incidence of MAC-Ts is high and approaches 100% as in the Burkitt lymphomas, indicating the importance of these translocations and the activation of c-myc in the pathogenesis of these lymphomas.

The relevant physiological functions of the c-myc gene are not yet understood. Only recently it has been shown that the protein product of the c-myc dimerizes with the product of the max gene to form a specific DNA-binding protein (43). Although c-myc transcription occurs throughout the active cell cycle (G1 to M), it undergoes a burst about 1 h after the cells move from G0 to G1 and then attains a lower but sustained transcription throughout G3 until mitosis (44). c-myc is no longer transcribed when the cell goes out of cycle as in the terminal differentiation of HL-60, several erythroleukemic cells, and 3T3-L1 pre-adipocyte lines (see Ref. 44). For several reasons it is thought that c-myc may be a transcriptional regulator (45) that is essential to committing the cell to a program of DNA synthesis and mitosis. Since c-myc probably acts throughout the G1 phase it may regulate several other functions relating to the progression through this part of the cycle. Possibly some of these permit cells to respond to exogenous growth or progression factors. c-myc down-regulation is an apparent requirement for terminal differentiation in other non-B-cell types; this is probably true for B-cells as well. c-myc dysregulation may serve to maintain cells in a proliferative cycling mode, but more critically for B-cells, it may block the ability of B-cells to enter a G0 state (45).

Aging. Aging is probably an important contributing factor in the pathogenesis of the Group I B-NHLs, since these tumors occur predominantly in older age groups, and the increase in the rates rose in each age group over 55 years (4). The underlying biological explanation for how aging influences lymphomagenesis is not yet well understood. The effect of aging on the immune system has been studied for a number of years. The concept that aging is an immunodeficient state may be too simplistic (46). A number of individual immunological deficits are now documented, but many components of immune responses are intact (46–50). New clonotypes may be expressed in the bone marrow (47). The net result as suggested by Russo et al. (46) is a dysregulation of the immune system.

First, it is well known that the thymus involutes and thus the T-cell repertoire depends more heavily on the peripheral pool. In addition, T-cell proliferation (48) and IL-2 production decrease (46). Autoreactive T-cells appear with increasing age (46). There is a striking reduction in older persons in the phytohemagglutinin responsiveness of peripheral blood T-cells, which are reduced to 30% of those seen in young subjects (48). The underlying mechanism is not yet clear, but Beckman et al. (48) have provided evidence that T-cells from elderly individuals are capable of responding to mitogens when artificially provided in vitro but that in vivo there is a defect in the ability of the T-cells to interact with accessory cells.

In the B-cell lineage humoral responses to foreign antigens decrease while production of autoreactive antibodies increases (46). Changes in the B-cell repertoires in mice occur with aging that may change VDJ gene selection (47). Human B-cells from old individuals proliferate 50% less efficiently than those from young subjects; these differences may be due to impairments in components of certain signal transduction pathways in B-cells (49, 50). Other deficits have been described in mice, including a defect in antigen transport and germinal center formation in old mice (51). Finally, it has long been known that the incidence of monoclonal gammopathies of undetermined significance increase dramatically with age (52). The formation of these lesions has been linked to some form of age-related T-cell immunodeficiency that can be augmented nonspecifically by intercurrent illness (52).

Thus aging is associated with imbalances in T- and B-reper- toires. The regulation of the size and proliferative activities of certain B-cell clonotypes in older individuals may be less well controlled because of the changes in the T-cell compartment. This, coupled with the increased frequency of autoreactive clonotypes, may produce a population of B-cells that is less subject to regulation by T-cells and which is at increased risk for further progress toward autonomous growth.

This raises epidemiological questions. Assuming there are potential lymphomagenic agents in the environment such as the herbicides and pesticides (6, 53), how would such exposures influence the incidence rates in various age groups? Would such agents affect all or only the older age groups? If as the very preliminary available data indicate the rate changes are predominantly in the older age group, one would then argue that the B-cells in older subjects are at greater increased risk of undergoing neoplastic transformation than B-cells from younger subjects.

Immunodeficiency. B-cell lymphomas (Group II) are associated with different forms of immunodeficiency. Lymphomas have appeared in an alarmingly high incidence in HIV-infected individuals (54, 55); these have sometimes occurred as the presenting manifestation of the disease. Most frequently the lymphomas develop in the immunodeficient state. Secondary lymphomas develop in relatively high frequency in genetic immunodeficiencies such as the Wiscott-Aldrich syndrome, ataxia telangiectasia (56), and other X-linked immunodeficiencies (57). Lymphomas are a well-known complication in posttransplantation immunosuppression by drugs (58, 59). Some of these lymphomas regress after withdrawal of the immunosuppressive drug (59). B-NHLs associated with immunodeficiency states are frequently oligoclonal or polyclonal, and this has raised the issue that some of these lymphomas represent lymphoproliferative rather than neoplastic disorders. Many of the lymphomas arising in the various forms of immunodeficiency are EBV+, suggesting the participatory role of EBV genes in the lymphomagenic process. The basic mechanism for lymphomagenesis in immunodeficiency is thought to involve a breakdown of immunological surveillance and the ability of T-cells to eliminate cells expressing atypical cell surface antigens.
EBV is associated with many of the Group II lymphomas; virtually 100% of endemic Burkitt lymphomas are EBV-positive, but a much lower frequency is seen in sporadic Burkitt lymphomas. The frequency varies in acquired immunodeficiency syndrome-associated NHLs and NHLs in other immunodeficient states. EBV is a ubiquitous viral infection in humans, and over 95% of adults are persistently infected (60). In developing countries virtually all children by the age of 3 have been infected (61). However, the virus does not produce obvious disease but does persist indefinitely. Viral persistence is maintained in two tissues, the nasopharyngeal epithelium and B-cells, but details of the mechanism are not yet established (60). In B-cells the virus is maintained as a plasmid in the cytoplasm of resting cells. A substantial number of B-cells are infected. Newly infected (nonneoplastic) B-cells and the immortalized lymphoblastoid cell lines that can be cultured from the blood of persistently infected individuals express multiple viral proteins EBNA1, 2a, 3a, 3b, 3c and EBNA-LP, LMP1, 2a, 2B but produce very little virus (60). These cells actively proliferate; however, their EBV-associated membrane proteins can be antigenic targets for cytotoxic T-cells. In normal individuals EBV production is held in check by active cellular and humoral immune mechanisms. Three different EBV—B-cell relationships that are associated with EBV latency have been recently described (60). In immunodeficient states this balance can be disrupted, and EBV-infected B-cells can begin to proliferate. Interestingly, Burkitt lymphoma cells express only EBNA-1 and therefore appear to escape immunological surveillance.

EBV many contribute to immortalization and growth dysregulation through the action of some of its genes on the B-cell genome. EBV infection is associated with changes in B-cell proliferative behavior. It has long been known that immortalized B-cell lines can be relatively easily established in vitro from the peripheral blood cells of persistently infected individuals. In recent rather dramatic studies Mosier et al. (62) and Rowe et al. (63) have shown that transplantation of peripheral blood cells from normal healthy persons with persistent EBV to severe combined immunodeficiency disease mice results in the development of transplantable lymphomas that kill their hosts. EBV genes then can contribute to abnormal B-cell growth and autonomy as defined by this system. It is a startling thought that most of us have cells in our blood with the potential for such abnormal growth.

Role of Antigenic Stimulation. Sustained or intense antigenic stimulation provided by the excessive production of antigens may play an important role in lymphoproliferation and in some group II lymphomas. Malaria and HIV infections are thought to not only provide intense antigenic stimulation but also to act as a continuing source of new antigens arising from antigenic variation of the infecting agent (61, 64). Both Malaria and HIV infections are associated with B-cell lymphoproliferation, which may be due to both specific antigens generated by the infectious agent and nonspecific mitogenic effects. Interestingly, both of these infections are associated with the formation of a relatively high number of extranodal lymphomas.

The role of antigenic stimulation in the Group I lymphomas is less well defined (65). The association of specific subsets of B-cells with certain lymphomas suggests that some populations of B-cells are at greater risk for lymphoma development. Examples are the B-cell chronic lymphocytic leukemias and diffuse small cleaved cell lymphoma (DL/CC lymphoma) that express CD5 surface antigen in a high percentage of cases (66, 67). A number of studies have shown that the Igs produced by B-cell chronic lymphocytic leukemia are autoreactive (see discussion in Refs. 68 and 69). In contrast follicular lymphomas do not express CD5, but many of the Igs produced by these tumors are also autoreactive (70). The CD5+ cells in the mouse are thought to be self-renewing, but is it clear yet whether the human CD5+ B-cell population is self renewal? Interaction with self-antigens may provide the stimulus for maintenance and self-renewal of these cells and increase the risk for developing oncogenic mutations.

Genetic Susceptibility. In humans there are striking variations in the incidence of different forms of NHL in Asia (71, 72), where there is a greater proportion of T-cell NHLs and a difference in the distribution of B-NHLs from those seen in the United States. Follicular or nodular lymphomas form a minor group in Asian countries (71, 72), while they comprise a large group in the United States. These findings raise the possibility that the genetic background influences the development of specific types of lymphomas. This is an area in need of investigation. There is evidence of genetic susceptibility to B-cell tumor formation in inbred strains of mice. Findings in transgenic mice bearing Eu-myc or Eu-v-abl (40) suggest that the genotype of the mouse can influence the rate of B-cell tumor formation or progression. In paraffin oil-induced plasmacytoma-agenesis in mice there are strong strain differences as well as evidence that specific genes determine susceptibility and resistance (73).

Summary

Chromosomal rearrangements are a major mutagenic mechanism in B-cell tumor formation. Other biological factors in human lymphomagenesis are aging, immunodeficiency, antigenic stimulation, and genetic predisposition. Future work should be directed toward understanding the factors that increase the rate of formation of illegitimate exchanges between genes and the underlying mechanisms of the biological factors.

References


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