Molecular Basis of Lymphomagenesis

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Abstract

Lymphoid neoplasms, like all malignant tumors, arise as a consequence of the accumulation, in a single cell, of a set of genetic lesions that result in altered proliferation or increased clonal life span. The most frequently observed genetic abnormalities among the malignant non-Hodgkin's lymphomas are translocations, which appear to be lineage- and, to a large extent, lymphoma specific. Recombinases that normally mediate the process of antigen receptor gene rearrangement appear to have an important (but not exclusive) role in the mediation of these translocations and of other types of gene fusion (e.g., deletion of intervening DNA). Frequently, such fusions result in the increased or inappropriate expression of crucially important proteins, many of which are transcription factors that regulate the expression of other genes. These abnormalities, however, do not appear to be sufficient to induce lymphoma, and it is likely that the additional genetic lesions required differ from one tumor to another.

The likelihood of any given clone of cells accumulating a sufficient number of relevant genetic lesions to give rise to a lymphoma is probably a function of its life span. Prolonged survival of a cell clone may be mediated by viral genomes (e.g., Epstein-Barr virus and human T-cell leukemia/lymphoma virus type 1), by the abnormal expression of cellular genes that inhibit apoptosis (e.g., bcl-2), or by the mutation or deletion of cellular genes that are necessary for apoptosis, e.g., p53. The background rate at which genetic lesions occur is amplified by the interaction of inherited and environmental factors, the latter appearing to be the major determinants of incidence rates. However, inherited factors that influence lymphomagenesis, including variability in the ability to repair DNA damage or in the fidelity of antigen receptor recombinases for their signal sequences, may be crucial determinants of which particular individuals in a given environmental setting develop lymphoma.

Introduction

The word "lymphoma," like many nosological terms in use today, was coined in an era when gross pathology and clinical characteristics were the only existing tools of disease taxonomy, such that the separation of one pathological entity from another was difficult and often impossible. The subsequent preeminence of cellular morphology as a means of lymphoma classification, which persists to the present, owes much to the seminal influence of Virchow in the mid-19th century (1). Morphology, however, is limited by its subjective nature, by its inability to provide insights into pathogenesis, and by its frequent lack of precision. Lymphoid neoplasms arising from different cellular lineages, for example, are sometimes indistinguishable at a morphological level. Slowly, our reliance upon form (appearances) is being supplemented by a new understanding of the functional derangements that give rise to neoplastic behavior, an understanding that has been made possible by the rapidly developing knowledge of the molecular basis of cell proliferation and differentiation in the lymphohemopoietic system. Today, we consider that lymphoid neoplasia arises as a consequence of genetic abnormalities, almost exclusively occurring in somatic cells, that lead to prolonged cell survival, to inappropriate growth, and, frequently, to a differentiation block. These molecular genetic abnormalities and their consequences surely provide the ultimate means of defining individual pathological entities, although a new classification scheme based on such abnormalities has yet to be proposed.

From this perspective, a lymphoid neoplasm may be defined as "the progressive accumulation of a clone of lymphoid cells which arises as a consequence of multiple genetic changes occurring in the cell genome." This definition would exclude the polyclonal lymphoproliferative processes that sometimes arise in patients with immunodeficiency syndromes, regardless of whether immunosuppression is iatrogenically induced, as in allograft recipients, inherited, or acquired. There is continuing controversy as to whether similar processes occur in HIV-infected individuals. These lymphoproliferative syndromes frequently arise as a consequence of failure of the immune system to control the proliferation of multiple clones of EBV-infected B-cells, rather than of intrinsic, biochemical abnormalities that result from genetic aberrations (2). While they may be clinically and morphologically indistinguishable from lymphomas, the essential difference in their pathogenesis is supported by the observation that a fraction of those that arise shortly after allografting will regress upon withdrawal of immunosuppressive therapy. When lymphoproliferative syndromes occur late after allografting, however, they are more likely to be unresponsive to withdrawal of immunosuppression and to contain detectable genetic lesions. In such cases it seems likely that a preceding phase of subclinical lymphoproliferation has led to the development of genetic abnormalities in a single cell clone, with outgrowth of a "true" lymphoma. Lymphomas that are not associated with EBV may also arise de novo in patients with various forms of inherited immunodeficiency or HIV infection (3).

It seems probable that a preceding phase of abnormal proliferation and/or of increased life span of one or more cell clones is a prerequisite for the development of lymphoma, and indeed, of all neoplasms, since neoplasia is the consequence, not of a single genetic change, but of many such changes. Preneoplastic clones must therefore survive long enough to accumulate all of the necessary genetic abnormalities for the emergence of the final pattern of growth that is manifested as a clinically apparent tumor (Fig. 1). It is because of the stochastic element in this process that neoplasms are nearly always monoclonal. This rule may be broken when the risk that the set of genetic lesions may accumulate in a single cell is very high, e.g., when at least one of the necessary genetic abnormalities is present in all cells (an inherited or germ cell mutation); when the degree of exposure or potency of one or more exogenous agents is sufficiently great that genetic changes occur in a high proportion of exposed cells; or when a single agent, e.g., a virus, is sufficient to cause malignancy or requires perhaps few additional genetic lesions. In practice, the occurrence of oligoclonality (i.e., the synchronous development of more than one malignant clone) is extremely rare, except in the immunodeficiency-related lymphoproliferative syndromes, and a more likely event is the occasional

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3 The abbreviations used are: HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; HTLV, human T-cell leukemia/lymphoma virus.
points in the differentiation process, the lack of a molecule essential to subsequent cellular function (or the possession of a forbidden molecule) triggers a process of programmed cell death whereby the cell enzymatically cleaves its own DNA into nucleosome-sized lengths. Known as apoptosis, this process must be very tightly regulated and doubtless involves multiple pathways and gene products. One gene that has been shown to be able to prevent apoptosis is bcl-2 (7), a gene that was discovered by cloning the region on chromosome 18 that is juxtaposed to immunoglobulin heavy chain sequences as a consequence of a 14;18 translocation. This translocation is present in a high proportion (60 to 80%) of follicular lymphomas, and the deregulated expression of bcl-2 is clearly an essential component of the pathogenesis of this disease. EBV and HTLV also cause persistence of the cell clones they infect, thus predisposing them to subsequent malignant change. In the case of HTLV-1 and HTLV-2, the tax gene transactivates several T-cell activation genes, including the genes for interleukin 2 and its receptor, thus establishing an autocrine loop (8). In the case of EBV, the recent demonstration that one of the EBV latent genes, the latent membrane protein, can induce bcl-2 may be pertinent to the persistence of EBV-infected B-cells (9), particularly since EBV-transformed B-cells are probably rapidly eliminated by EBV-specific, HLA-restricted, cytotoxic T-cells. Perhaps the true EBV reservoir is a bcl-2-expressing memory B-cell which fails to express those EBV antigens that provoke T-cell cytotoxicity. Interestingly, p53, an antioncogene, has been shown to be necessary for apoptosis to occur, and its loss (e.g., by mutation or deletion) may, in some circumstances, lead to prolonged cellular life span (10).

Implications of the Need for Multiple Genetic Lesions

These considerations have a number of implications which can be summarized as follows. (a) The life span of a cell clone must be sufficiently long to permit the accumulation of the several genetic lesions that lead to neoplasia. (b) The accumulation of genetic lesions is more likely to occur in cells that are actively proliferating. (c) The risk of the development of genetic change increases as the degree of genetic instability increases. (d) Cure of the neoplasm does not necessarily lead to eradication of cell clones with subneoplastic genetic changes.

Life Span. A cell destined to become malignant must either be of a type that undergoes essentially permanent self renewal (i.e., it possesses one of the characteristics of stem cells), or its life span must be prolonged by one of the first (if not the first) genetic lesion to occur, including viral infection. In the lymphoid system highly efficient mechanisms exist for the elimination of cells which develop either an unwanted antigen specificity (e.g., "self") or fail to synthesize a functional antigen receptor (immunoglobulin, in the case of B-cells). At specific
the inflammatory process itself may increase the risk of genetic damage because of increased generation of free radicals (see below). In some immunodeficiencies, such as the Wiscott-Aldrich syndrome, repeated occurrences of serum monoclonal gammopathy lasting for several months indicate that individual clones may occasionally become large enough for the immunoglobulin they produce to become apparent above the background of polyclonal immunoglobulin production. Such clones are likely to be at considerably increased risk for the development of a neoplasm.

Follicular lymphomas and other “low-grade” lymphomas often have long periods during which they are entirely subclinical and, even when clinically apparent, they may have a prolonged natural history and sometimes undergo spontaneous regression (12). This, coupled to the tendency of follicular lymphomas to transform into more aggressive tumors (which have been shown to express the same immunoglobulin idiotype as the preceding follicular lymphoma) (13) and to the existence of de novo large cell lymphomas that contain the same 14;18 translocations present in follicular lymphomas, suggests that these tumors represent a point on the spectrum somewhere between preneoplastic and fully neoplastic. They do appear to be able to respond to normal B-cell growth signals, e.g., from CD4-positive cells (13).

Genetic Instability. Another element that is relevant to the development of genetic changes in potential cancer cells is genetic instability. Today, the dynamic nature of DNA is well recognized and is clearly an essential component of not only such processes as DNA replication (which requires the cleavage and resplicing of DNA by topoisomerases as well as sequence “editing” during DNA polymerization), meiotic recombination, and the rearrangements of antigen receptor genes, but also evolution. Indeed, one of the tools of evolutionary variation appears to be the reshuffling of functional modules, such that, for example, a given catalytic element, when coupled to protein moieties with different cellular localization signals or different binding properties, or to different transcriptional elements, may be expressed at a different phase of differentiation or in a different cell lineage or alter its range of substrates. At a different level, genes must retain their integrity in spite of continuous DNA damage arising, for example, from free radicals released during intermediary metabolism or inflammatory responses or from exposure to environmental agents. Clearly, there is an absolute necessity for powerful and very tightly regulated enzyme systems to mediate essential genetic rearrangements and to repair DNA damage. Conversely, it is entirely feasible that genetic changes leading to decreased stability of DNA are an essential component of neoplasia, and variation in the regulation of these processes may well be one element that is responsible for the different propensities of individuals to develop cancer. This notion is supported by the increased incidence of malignant lymphomas in those suffering from disorders associated with spontaneous chromosomal breakage, perhaps related to defective DNA repair, such as Bloom’s syndrome, Fanconi’s anemia, and ataxia telangiectasia (14), although immunological deficiency is almost certainly a contributing factor in such individuals.

Subneoplastic Genetic Changes. It seems quite probable that genetic lesions capable of contributing to the neoplastic state, but insufficient to cause neoplasia by themselves, occur relatively frequently in persons who never develop neoplasia. This is supported by several lines of evidence. Mutations in recognized preneoplastic lesions, such as colonic polyps and oral leukoplakia, are well described (15, 16) while, in the context of lymphoid neoplasia, the recent finding, in hyperplastic but otherwise normal lymphoid tissue, of rearrangements of the bcl-2 gene similar to those associated with follicular lymphomas (17) strongly supports this idea. Moreover, this finding is consistent with the notion that an early genetic change may lead to prolongation of the life span of the affected clone and also implies that 14;18 translocations are insufficient, in themselves, to cause cell transformation. In the absence of an endogenous or exogenous stimulus to proliferate, 14;18-containing cells may rapidly enter a resting state (i.e., they are virgin lymphocytes or memory cells). It is tempting to speculate that the clinical appearance (or recurrence) of low grade lymphomas may be a consequence of the activation of a genetically altered memory cell of a genetically altered memory cell, doomed to persist because of bcl-2 expression, by exposure to antigen (or perhaps repeated antigenic activation of the same cell done over many years). Additional genetic lesions may be more likely to be acquired during these periods of activation. If this were true, it would imply that only 14;18-containing cells that repeatedly encounter antigens able to stimulate them will lead to follicular lymphomas. Follicular lymphomas appear to express the full B-cell repertoire of variable regions (13), so the chances that an encounter with an activating antigen will occur in the lifetime of an individual may be low and not inconsistent with the incidence of follicular lymphomas.

Follicular lymphomas also provide support for the possibility that successful treatment of lymphomas could result in the elimination of the fully transformed clone, but permit the persistence of cell clones containing less than the full complement of genetic abnormalities required for neoplasia. Recently, it was reported that cells bearing 14;18 translocations (detected by polymerase chain reaction) can be detected in long-term survivors (10 to 15 yr) of localized follicular lymphoma (18). Such cells either represent “dormant” lymphoma cells, possibly awaiting activation by the relevant antigen, or, more likely, belong to a premalignant clone which will only become malignant if additional genetic lesions are accrued.

Nature of the Genetic Lesions Associated with Lymphoid Neoplasia

The genetic lesions that occur in the lymphomas are, to a high degree, lineage and probably also differentiation stage specific. There are two explanations for this. (a) It appears highly probable that only genes that are transcribed (i.e., in regions of open chromatin structure, providing enzymes with access to the DNA) are susceptible to genetic damage, and (b), in any given lineage, only a finite set of genetic abnormalities will be relevant to the development of neoplasia.

The factors which govern whether a genetic lesion will arise in an individual are multiple and include the total number of susceptible cells in the individual, the life span of the cells, their proliferative state, the relative efficiency (inherited) of such processes as DNA repair and antigen receptor gene rearrangement (see below), the ability to scavenge endogenously or exogenously generated free radicals, and the presence of environmental factors that may alter any of these attributes or cause DNA damage directly. Ultimately, however, there are two major considerations: the nature of the genetic changes and the genes that are involved. The types of genetic abnormality that can occur include point mutation, deletion or insertion, gene amplification, and gene fusion. Gene amplification has not, to
date, been shown to be a common genetic abnormality in lymphoid neoplasia, and it will not be discussed further.

**Mutation.** Point mutations, and some kinds of deletion and insertion, are usually generated by interaction of DNA with highly active (i.e., charged) radicals, either of intracellular or extracellular origin. To a degree, the origin of the damage can be deduced, since endogenously generated mutations are usually transitions (i.e., substitution of one pyrimidine base for another or one purine for another), while exogenously generated mutations tend to be transversions (i.e., substitution of a purine for a pyrimidine or vice versa). Exogenously induced mutations can also be inferred from the high frequency of a specific mutation in tumors from patients from the same geographical region or subpopulation, but a low frequency of the same mutation in the same tumor type from a different population. An excellent example of a point mutation that is very likely to have been exogenously induced is the G to T transversion that occurs in codon 249 of the p53 gene in hepatocellular cancer from South Africa and China, but not in hepatocellular cancer from Taiwan and Japan (19, 20, 21).

It is perhaps pertinent, in this context, to point out that cancer chemotherapy entails the use of agents that are highly mutagenic. As such, it is not surprising that these agents have been incriminated in the production of second malignancies, notably in Hodgkin's disease, but also in a number of other tumors (22, 23). However, the possibility that the emergence of a second tumor results from the accumulation of additional genetic changes in a premalignant clone of cells that has not been eliminated by treatment, and which is environmentally induced or constitutional, should always be considered. That this possibility is real is demonstrated in familial cancers, where the same genetic lesion may predispose to more than one type of tumor, for example, the occurrence of osteosarcoma in patients who survive familial retinoblastoma (24), or the occurrence of multiple tumor types (sarcomas and carcinomas) in families with inherited p53 abnormalities, one of the lesions responsible for the Li-Fraumeni syndrome (25, 26).

**Gene Fusion.** Gene fusion (i.e., the fusion of one gene or part of a gene with another or part of another) occurs as a result of deletion of intervening DNA or inversion of a segment of a chromosome (when both involved genes are on the same chromosome) or chromosomal translocation (when the relevant genes are on different chromosomes). In the lymphoid system, such processes quite frequently bear the molecular hallmarks of being mediated by the recombinases that are normally involved in the process of antigen receptor gene rearrangement. Consistent with this is the tendency for the genes that define lymphoid cells, namely, these same antigen receptor genes (immunoglobulin and T-cell receptor genes), to be involved in the genetic fusions that are so characteristic of different types of lymphoma (27). In part, this may relate to the fact that the antigen receptor genes must undergo recombination of variable and constant region coding segments in order to generate functional antigen receptor molecules and to give rise to the required diversity of antigen binding sites. Regions of DNA that are to be recombined must be accessible to the enzyme systems that mediate the recombinations and are therefore more likely to be the sites of DNA breakage and religation. The process of antigen receptor gene rearrangement is essentially continuous and involves very large numbers of cells. In the B-cell lineage alone it has been calculated that, in humans, some $5 \times 10^{10}$ cells are generated each day from $5 \times 10^6$ precursor cells (28). Only $5 \times 10^6$ cells enter the B-cell pool, the rest presumably being eliminated by apoptosis.

The existence of a mechanism for cutting and splicing DNA carries with it a risk that the wrong regions will be cut and spliced. Since the consensus signal sequences that are adjacent to the DNA segments that must be spliced together as part of the normal process of antigen receptor gene rearrangement are also found quite widely distributed throughout the genome, it is not difficult to envisage that genes with no known relationship to antigen receptor genes may sometimes be spliced together at that time in cellular differentiation when antigen receptor recombinases are expressed. Indeed, this has been shown to be so in the case of the gene known as tal-1 or scl, situated on chromosome 1, which is fused with a gene that has been named sil (scl interrupting locus), also on chromosome 1, by the deletion of intervening DNA in some 20 to 30% of T-cell acute lymphoblastic leukemias (29, 30). While this particular genetic abnormality, like physiological antigen receptor gene rearrangement, is intrachromosomal, it has been shown that antigen receptor recombinases are able to mediate interchromosomal recombinations (31). Thus, the antigen receptor gene recombinases are at least capable of mediating the most obvious genetic lesions in lymphoid malignancies, chromosomal translocations (27, 32). However, recombinase signal sequences have not been detected at translocation breakpoints in all translocations occurring in lymphoid neoplasia. Whether these enzymes mediate translocations believed to occur close to the timing of antigen receptor gene rearrangement during cell differentiation, even if recombinase signal sequences are not evident, is a debated issue.

One of the implications of the possible mediation of gene fusion by antigen receptor gene recombinases is the necessity that such genetic aberrations must occur early in lymphoid differentiation, i.e., during that phase of differentiation when the recombinases are present in the cell. The stage at which the recombinases first appear has not been precisely identified. Since regulation of their function is probably through access to specific genes via alterations in chromatin structure, they are likely to be expressed before a cell actually undergoes physiological recombination of antigen receptor genes. Pathological recombination at this early stage of differentiation and resultant deregulation of the expression of a gene which may be appropriately expressed at this early stage may lead to its subsequent inappropriate expression as the cell undergoes further differentiation. This scenario is much more likely than fusion occurring at a differentiation stage when one of the genes is not normally expressed; fusion is intuitively unlikely when one of the partners is protected by a closed chromatin structure. If a genetic fusion has occurred that results in continued expression of genes that induce proliferation, the cell may only be recognized as neoplastic at the point in the differentiation pathway when its proliferation should normally cease, perhaps several steps beyond the stage in which the genetic change occurred. A mutation in a gene that prolongs the life span of a cell, but does not influence proliferation, may result in the accumulation of cells at a terminal stage of differentiation, or at a point where further differentiation requires an external signal (e.g., antigen).

It is not necessary to surmise that all instances of gene fusion are mediated by recombinases that normally mediate antigen receptor gene rearrangements. Other enzyme systems exist whereby genetic recombination can occur, for example, those that mediate the excision and reinterpolation of mobile genetic elements (e.g., transposons) and viral sequences. The possible
role of such recombinases in cellular gene fusion pertinent to neoplasia is largely unexplored.

Consequences of Genetic Abnormalities

The repertoire of genetic abnormalities that occur in lymphoid neoplasia is constrained by functional considerations. In any given cell type, only certain functional changes have relevance, and it is genes whose altered function can contribute to neoplasia that are referred to as oncogenes (genes whose expression normally promotes growth and which are associated with cancer when there is an enhancement of function) and as antioncogenes (genes whose expression normally inhibits growth and loss of function is associated with cancer). The terms "oncogene" and "antioncogene" are correctly applied only in the context of pathologically altered function. In practice there are three general types of functional change to consider: enhancement; inhibition; and alteration of a function. A variety of genetic lesions may result in inactivation of a gene, including a wide range of intragenic lesions, deletion of the gene, or altered expression of a second gene that regulates its transcription. Enhancement of activity is the result of a much smaller subset of genetic lesions, since they must be quite specific. Such lesions may cause altered expression of a gene that normally regulates the first, juxtaposition to heterologous enhancer sequences or to the promoter of another gene (sometimes resulting in a fusion protein), deletion or mutation of the regulatory region of the gene, or mutation of those regions of the protein product that are related to its enzymatic or protein binding properties. The inappropriate expression of a gene (e.g., at a stage of differentiation or a phase of the cell cycle when it should not normally be expressed), or lack of its expression, may lead to altered growth, prolonged life span, or inhibition of differentiation.

Deregulation of Transcription Factors and Genes Affecting the Cell Cycle and Life Span

Genetic abnormalities associated with lymphomagenesis frequently, but not invariably, result in the deregulation of putative or proven transcription factors such as c-myc, pbx, the rhombotin genes, and scl (tal-1) (33–36). Clearly, such genes may affect a broad variety of molecules involved with any and every facet of the life of the cell, including proliferation and differentiation. Expression of the c-myc gene, for example, appears to be associated with the ability of the cell to enter the cell cycle, i.e., to be "competent" to undergo DNA replication. There are two major mechanisms whereby such genes are deregulated: juxtaposition to regulatory elements derived from an antigen receptor gene and the formation of a fusion gene.

Role of Antigen Receptor Genes in Deregulation. A repetitive theme in lymphoid neoplasia is the presence of a chromosomal translocation involving an immunoglobulin or T-cell antigen receptor locus on one chromosome and a transcription factor on the partner chromosome. It seems highly probable that the transcription factor is then regulated as if it were the antigen receptor gene (Fig. 2A). In some cases, structural damage is present in the regulatory region of the transcription factor in addition to it being juxtaposed to an antigen receptor gene. Such abnormalities may be relevant to the usurpation of its regulation by enhancer regions within the antigen receptor locus (37).

Hybrid Transcription Factors. A second theme that is frequently observed in lymphoid neoplasia is the fusion of two genes coding for transcription factors. In this circumstance, the fusion protein is expressed as if it were the upstream partner, which bears the regulatory regions, including promoters, that now govern the expression of the fusion gene. The pattern of DNA binding, however, is probably determined by the downstream partner (Fig. 2B). In effect, the genes regulated (up or down) by the downstream transcriptional factor will be so regulated at a time in the differentiation process, or possibly cell cycle, when the upstream gene is normally expressed, rather than when the downstream component is normally expressed. It requires little imagination to see what damage could be wrought by the inappropriate expression of a gene that controls the expression of many other genes. In some cases, inappropriate expression of genes, even though they are irrelevant to the neoplastic state, may account for the aberrant immunophenotypes that are sometimes seen in lymphoid neoplasms.

Deregulation of End-Function Genes. While inappropriate expression of transcription factors could result in a wide range of aberrant functional consequences, only a limited number of such aberrations would be relevant to neoplasia, including alterations in the regulation of proliferation, differentiation, and life span. Abnormal expression of genes that participate in
Altered Function of Genes Involved in Cellular Proliferation and Differentiation

In addition to the deregulation of the expression of genes that regulate vital cellular processes, the function of the genes that directly mediate these processes may be modified by genetic changes. In this case, the protein product of the gene may be affected such that there is either a loss of function (e.g., in the case of genes that are necessary for apoptosis to occur or that inhibit cellular proliferation or promote differentiation) or an increase in function (e.g., in the case of genes that inhibit apoptosis or differentiation or promote cellular proliferation). A large number of genes are involved in these processes, many of which have already been recognized as oncogenes or oncoproteins. Detailed reviews have been provided elsewhere (40, 41).

Brief, oncogenes include molecules capable of functioning as ligands for growth factor receptors (e.g., sis), as activated growth factor receptors present on the cell surface (e.g., erbA and erbB), as activated signal transducing molecules, normally associated with the cytoplasmic aspect of the cell membrane (e.g., ras), as cytoplasmic signalling molecules (e.g., src) or as transcription factors (e.g., myc, myb, fos, jun, pbx, rom-1, and romom-2) normally present in the cell nucleus. Not surprisingly, abnormalities of genes involved in the same functional pathway may give added or synergistic pathological effects. Oncogenes include the retinoblastoma gene, rb, the Wilms' tumor gene, and the gene involved in carcinoma of the colon. Only mutations in the rb and p53 genes have so far been described in lymphoid neoplasia (42).

The Special Case of p53. The p53 gene is a special case because it appears to be able to contribute to neoplasia in two modes, either as an oncogene or an antioncogene (43, 44). This is probably a consequence of the type of mutation that occurs in this gene, for some mutations result in loss of function (namely, its ability to inhibit cellular proliferation) and some in the gain of a new function (e.g., the binding of a heat shock protein, HSC70, although the significance of this to oncogenesis is unclear). There is no doubt that p53 plays an important role in the inhibition of cellular proliferation and has different conformational forms that it assumes in different phases of the cell cycle (45). Some mutations may result in its assuming permanently a conformation that should normally be present only transiently, during a specific phase of the cell cycle, and it may then be unable to inhibit cellular proliferation. It has also been shown in experimental systems that some mutated forms of p53 can co-operate with ras genes in the induction of malignant transformation. While it has been postulated that this is a dominant negative effect, i.e., the mutated protein simply binds to and consequently inactivates the normal protein, thus preventing inhibition of cellular growth, this may be an oversimplification. Apart from its relevance to cellular proliferation, mutations in p53 could affect several pathways relevant to lymphomagenesis. p53 appears to be required for normal B-cell differentiation (46) as well as for apoptosis (10), and its lack (e.g., by "loss-of-function" mutations) could thus impair differentiation and lead to prolonged life span. Mutation may also be relevant to the emergence of chemotherapy-resistant clones, since induction of apoptosis appears to be one mechanism whereby cells are killed by chemotherapeutic agents (47). Thus, lack of p53 could lead to lack of chemotherapeutic efficacy by preventing apoptosis. In addition, mutated p53 has been shown to transactivate the mdr-1 gene involved in pleiotropic drug resistance, whereas wild type p53 may suppress mdr-1 (48).

p53 mutations appear to be relatively uncommon in lymphoid malignancy. Only the small noncleaved cell lymphomas frequently possess p53 mutations (30% in primary tumors and 70% or more in derived cell lines). Diffuse small cell lymphomas and chronic lymphocytic leukemia have p53 mutations in a small percentage of cases (49, 50).

Association of Specific Genetic Lesions with Particular Lymphoma Subtypes

The phenotype of a cell results from the expression of a limited set of genes, and somatic genetic changes of consequence are not only more likely to occur in these genes, because of their open chromatin structure, but are unlikely to affect the cell if they occur in genes that are not expressed. Moreover, different genetic changes will have different cellular consequences, e.g., deregulation of myc causes continued proliferation, whereas deregulation of bcl-2 prolongs life span. It is not, therefore, surprising that a number of distinct pathological entities can be defined, each of which has a characteristic histological appearance, immunophenotype, nonrandom chromosomal translocation (Fig. 3), and clinical behavior pattern. In addition, each lymphoma can be reasonably well equated with a particular normal counterpart cell (Figs. 4 and 5). This statement needs to be qualified by the recognition that what appear to be identical chromosomal translocations can occur in morphologically different lymphomas. It is important to note that this is not the case for lymphomas that are of different cell lineage. Within a lineage, however, the same translocation may appear in tumors with different histology, e.g., 8-14 translocations in small noncleaved cell lymphomas and a subset of diffuse large cell lymphomas, and 14;18 translocations in all histological categories of follicular lymphomas (including small, mixed, and large cell) as well as a subset of diffuse large cell lymphomas and small noncleaved cell lymphomas (51, 52).

There are several possible explanations for these findings. For one thing, there is a morphological continuum between small noncleaved cell lymphomas and large cell lymphomas (53), on the one hand, and small, mixed, and large cell follicular lymphomas on the other (54). This morphological, as well as genetic, similarity implies that the lymphomas in each series may be closely related to each other with respect to their pathogenesis. Interestingly, there is evidence that there is a genetic spectrum too, the translocations of different histological subtypes varying with respect, for example, to the locations of chromosomal breakpoints (55, 56). It is entirely possible that the associated genetic lesions also differ. Indeed, in lymphomas.
Genealogical consequences of the translocation have relevance limited to one enzymes that mediate the translocation may be differentiation stage specific, and (c) the functional consequences of the translocation have relevance limited to one and possibly to only a particular range of differentiation stages. The hypothetical multipotential cell shown here is able to differentiate into T-cell lineage and possibly to only a particular range of differentiation stages. The type, because (a) the level and pathway (lineage) of differentiation determine the particular phenotypes. Each translocation is more likely to arise in a specific cell lymphoid lineage and the association of specific chromosomal translocations with phoma (MZL), and small cleaved cell lymphoma (SCC). PB, pre-B-cell; VL, virgin lymphocyte; AL, activated lymphocyte; MC, memory cell; and PC, plasma cell.

Correlation of Pathological Anatomy, Clinical Features, and Genetic Abnormalities

While there is much to be learned of the genetic lesions associated with lymphoid neoplasia, a clear pattern is beginning to emerge. The broad distinctions of low, intermediate, and high grade lymphomas made by the National Cancer Institute Working Formulation are somewhat artificial, since there is considerable overlap between the intermediate and high grade categories with respect to clinical behavior. There do seem to be, however, more and less aggressive groups, based on their clinical behavior, even though within these groups there is a rather broad spectrum of aggressiveness. Follicular lymphomas and small cell lymphomas, for example, which fall into the low grade category, are compatible with long survival, even with minimal or no therapy. Patients with these forms of lymphoma usually die as a result of conversion of the lymphoma to a more aggressive form, or from the complications of treatment rather

MOLECULAR BASIS OF LYMPHOMAGENESIS

Fig. 3. Diagrammatic depiction of differentiation pathways of cells of the lymphoid lineage and the association of specific chromosomal translocations with particular phenotypes. Each translocation is more likely to arise in a specific cell type, because (a) the level and pathway (lineage) of differentiation determine the chromatin pattern in DNA regions that may be involved in a translocation, (b) enzymes that mediate the translocation may be differentiation stage specific, and (c) the functional consequences of the translocation have relevance limited to one and possibly to only a particular range of differentiation stages. The hypothetical multipotential cell shown here is able to differentiate into T-cell precursors, in which chromosome translocations involving the T-cell antigen receptor genes (14q11, a and b; 7q35, lì; and 7q13, v) can provide a critical lesion in the pathogenesis of T-cell acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL), or into B-cell precursors in which chromosome translocations involving the immunoglobulin heavy chain genes on chromosome 14q32 provide a critical lesion for the development of various B-cell neoplasms, including small noncleaved cell lymphoma (SNC), large cell lymphoma (LC), mantle zone lymphoma (MZL), and small cleaved cell lymphoma (SCC). PB, pre-B-cell; VL, virgin lymphocyte; AL, activated lymphocyte; MC, memory cell; and PC, plasma cell.

where more than one genetic lesion has been described, one of the lesions may be present in only a subset of tumors (e.g., p53 mutations in small noncleaved cell lymphomas (49, 50)). In the case of follicular lymphomas, the development of additional genetic lesions (e.g., an 8;14 translocation, or simply more aneuploidy) is associated with histological evolution from follicular to diffuse morphology—a form of evolution rather like a blast crisis in chronic myeloid leukemia. These transformations are associated with a rapid downhill clinical course (57–59). It is probable that similar considerations apply to more aggressive (intermediate or high grade lymphomas), although this is less obvious because, as a group, their behavior is readily distinguished from that of the low grade lymphomas. However, the clinical course of individual patients with diffuse aggressive lymphomas varies quite markedly, and recurrent tumors may proliferate much more rapidly than primary tumors. We may conclude that the borderline between one type of lymphoma and another, arising from the same lymphoid lineage, is often blurred, both with respect to histology and genetic abnormalities, although broad distinctions can quite readily be made. We should not, perhaps, be surprised at this, since the distinctions made between the differentiation stages of normal lymphoid cells are similarly somewhat artificial. The use of genetic lesions for taxonomic purposes does, however, have the advantage of greater objectivity. In addition, subsets of histologically identical tumors (e.g., follicular lymphomas with and without a 14;18 translocation or molecular variants of the small noncleaved lymphomas) can be readily distinguished (60, 61). Whether these different subsets of tumors behave differently at a clinical level, or have a different response to treatment, remains to be determined.
than from the underlying process itself. Interestingly, to date there is no convincing evidence that any patient with more than localized low grade lymphoma has been cured. On the other hand, patients with intermediate or high grade lymphomas usually have a very rapid clinical course if untreated, but respond well to chemotherapy and can be cured in a high proportion of cases (60% or more).

There are clearly basic differences in the types of genetic lesions that are associated with low grade lymphomas and those associated with intermediate and high grade lymphomas. The former result primarily in the slow accumulation of neoplastic cells in anatomically appropriate areas. Thus, follicular lymphomas and high grade lymphomas are, for the most part, confined to the reticuloendothelial system, including the lymph nodes, liver, spleen, and bone marrow. Moreover, the architecture of the cellular accumulation bears a considerable resemblance to that of the normal counterpart cells. Follicular lymphomas are so called because of their histological and phenotypic similarity to normal secondary follicles in lymphoid tissue, while mantle zone lymphomas often assume a quasifollicular pattern quite consistent with the immunophenotypic resemblance of these lymphomas to the cells which normally compose the primary follicles and the mantle zone of secondary follicles (39).

Low grade lymphomas tend to be widely disseminated (less than 10% are localized at presentation), consistent with the recirculation of their normal counterpart cells through the lymphoid tissue. Moreover, they retain, in large measure, the migratory and homing characteristics of their normal counterpart cells. Indeed, there is evidence that the follicular pattern of follicular lymphomas is dependent upon the presence of dendritic reticular cells, which are always present in both normal and neoplastic germinal follicles (62). Interestingly, there is good evidence that the chromosomal translocation associated with the majority of follicular lymphomas, (t(14;18), occurs close to the time of immunoglobulin gene rearrangement (the breakpoint occurs at a J region adjacent to a heptamer-nonamer signal sequence), suggesting that the neoplastic clone undergoes differentiation prior to its manifestation as a tumor. It would, therefore, appear that the central abnormality of the neoplastic clone in low grade lymphomas is a tendency to abnormal accumulation at a specific stage of differentiation (in the case of mantle zone and follicular lymphomas, at the stage of recirculation through lymphoid follicles). This is entirely consistent with the deregulation of the bcl-2 gene that is the consequence of the 14;18 translocation (although this translocation is probably insufficient, by itself, to induce a lymphoma). Perhaps all low grade lymphomas result from genetic lesions that have a similar functional consequence.

In contrast to the low grade lymphomas, other lymphomas are associated with more aggressive growth and less adherence to the anatomical distribution of the presumptive normal counterpart cell, although high grade lymphomas manifest evidence of some retention of the migration characteristics of their lineage, e.g.: the frequent involvement of the thymus in lymphoblastic lymphoma, the neoplastic counterpart of precursor T-cells and of the skin in several T-cell lymphomas of peripheral T-cells, e.g.: mycosis fungoides, Sézary syndrome, and the T-cell lymphoma associated with HTLV-1 (Fig. 4). Spread beyond lymphoid tissue is much more frequent and extranodal lymphoma is common; almost invariably the case in small noncleaved cell lymphomas, for example. This may reflect in part the stage of differentiation of the predominant tumor cells and in part a greater departure from the controlling influence of growth factors and homing receptors. It seems likely that the basic lesion of the more aggressive lymphomas is retention of the ability to proliferate regardless of the differentiation stage and development of a greater degree of autonomy than the low grade lymphomas. Autonomy, however, is relative. Clinical evidence suggests that growth factors may influence the likelihood that a lymphoma will grow in certain anatomical locations. In Burkitt's lymphoma, for example, there is a very high propensity of the tumor to grow in the developing molar tooth buds of young children in Africa and to involve the breasts of pubertal and lactating females (63).

Interaction of Environmental Factors with the Cell Genome in Lymphomagenesis, as Exemplified by Burkitt's Lymphoma

Variations in the incidence of specific types of lymphoma throughout the world, or even in different populations within a single country, demonstrate that the development of a malignant lymphoma is not due to chance alone. There is little doubt that both inherited and environmental factors are important, although the latter may be the major determinant of incidence in a given geographical region. Perhaps the genetic background of a subset of individuals in any population leads to heightened susceptibility to lymphoma when exposed to relevant environmental factors. Relevant environmental factors include microorganisms, mitogens (e.g., phorbols), DNA damaging agents (e.g., chemicals), and immunosuppressants (e.g., malaria, virus infections, or drugs). Microorganisms may be important by virtue of their immunogenic or mutagenic properties (e.g., through causing inflammation and free radical generation) or, in the case of viruses, via direct action on cellular genes or their protein products.

The variations in the incidence of different types of non-Hodgkin's lymphoma with age provide a number of insights into lymphomagenesis. For example, low grade lymphomas, the essential characteristic of which is the slow accumulation of abnormal cells, essentially never occur in young children and are rarely observed before the age of 25 yr. On the other hand, children may be more likely to develop highly proliferative neoplasms that originate in lymphoid precursor cells, perhaps because the total number of such cells is higher in the first decade of life (as evidenced by, for example, the size of the thymus). The late appearance of follicular lymphomas may simply be a consequence of the time required for a sufficient number of genetic lesions to accumulate (a likely probability in view of the finding of rearranged bcl-2 genes in normal tonsils in children), for sufficient numbers of lymphoma cells to accumulate, or both. Follicular lymphomas are also quite uncommon in developing countries (19). Whether the risk of transformation into an aggressive tumor (i.e., as a consequence of additional genetic changes) is higher in the setting of a developing country, such that a clinical phase of a low grade lymphoma is rarely seen, or whether the bcl-2 translocation (or one of the additional genetic lesions required for the development of low grade lymphoma) rarely occurs in the developing countries remains unknown. The various factors that influence the development of a lymphoma are summarized in Fig. 6.

It is reasonable to assume that, while the degree of exposure to environmental factors may vary markedly, even in the same geographical region, the stochastic element in lymphomagenesis is the major explanation as to why not all individuals with the same environmental exposure develop a tumor. Burkitt's lymphoma provides an excellent paradigm to explore further.
MOLECULAR BASIS OF LYMPHOMAGENESIS

Fig. 6. Diagrammatic depiction of the factors that influence the risk of developing lymphoid neoplasia. These include inherited genetic factors which may include mutations in genes relevant to the pathogenesis of cancer particularly in antioncogenes, spontaneous chromosomal breakage and defects in DNA repair, or immunodeficiency syndromes. Age presumably influences the absolute numbers of target cells for pathogenetic events, and various environmental factors may induce hyperplasia of specific cell populations and/or genetic abnormalities.

the interaction between the environment and the cells of the immune system.

Burkitt and his colleagues (63) demonstrated that, in equatorial Africa, where the incidence of the tumor is relatively high, the distribution of Burkitt's lymphoma is climatically determined; an early observation was the coincidence of its distribution with that of mosquito-vectored diseases such as yellow fever, O'Nyong Nyong, and malaria. This led to the hypothesis that Burkitt's lymphoma may be caused by a virus transmitted by insects, a hypothesis that led directly to the discovery of EBV in cell lines derived from tumor samples obtained from African patients. Until recently, in spite of the subsequent demonstration that some 95% of African Burkitt's lymphomas contain EBV DNA, there was no evidence that the virus was causally associated with the pathogenesis of the disease. Indeed, the recognition that Burkitt's lymphoma in temperate countries is not required in others. The observation that there are differences result in clinical differences (63). Remarkably, there appear to be molecular subtypes of Burkitt's lymphoma. It is probable that EBV contributes to some of these subtypes, but is not required in others. The observation that there are differences in the incidence and clinical features of the tumors in tropical and temperate zones suggests that the molecular differences result in clinical differences (63). Remarkably, there appear to be two "gradients" that can be discerned with respect to EBV association and chromosomal breakpoint location. This is exemplified by the characteristics of the tumor in Africa (Ghana), North America (the USA), and South America (Argentina, Chile, and southern Brazil). Most equatorial African tumors have breakpoints far away from the c-myc gene on chromosome 8, while most North American tumors have breakpoints close to or within the c-myc gene. South American tumors appear to be a mixture of these two types, but many tumors in Argentina have breakpoints in an intermediate position (Fig. 7). Similarly, EBV association is 95% in Africa, 20 to 30% in the USA, and some 50 to 60% in South America (60, 64). These relative figures do not do justice to the very large differences in incidence of Burkitt's lymphoma subtypes in different world regions. The subtype most common in Africa (approximately 75% of cases) has an incidence some 70 to 100 times higher in Ghana than in the USA. In contrast, the molecular variants common in the USA may have a similar or only slightly increased incidence in Africa.

It is not known precisely how the geographical location can influence both the site of the chromosomal breakpoints and the presence or absence of EBV DNA in the tumor cells. As more information accumulates, however, an overall picture is beginning to emerge, even though the molecular events relevant to pathogenesis will, of necessity, always remain hypothetical (37).
The primary molecular genetic abnormality is the chromosomal translocation which results in the juxtaposition of c-myc to immunoglobulin sequences and the consequent expression of the c-myc gene as if it were an immunoglobulin gene. In a cell of the B lineage, this effectively means continued expression of c-myc and maintenance of the cell in a proliferative phase. There is evidence that the translocations occur in immature B-cells, close to the time of (27) or even before immunoglobulin gene rearrangement. It seems probable, from the epidemiological evidence, that the chromosomal breakpoint location is determined largely by environmental factors. While there is no evidence that EBV can influence the breakpoint location, other environmental agents (e.g., microorganisms or plant products such as phorbol esters) may be able to do so, perhaps by influencing the numbers of B-cells at various stages of differentiation. Malaria, in fact, has been shown, in mice, to cause an increase in the rate of production of B-cell precursors, particularly early and intermediate pro-B-cells, and increased precursor B-cell loss (65). Purely on a statistical basis, this could increase the risk of a genetic abnormality occurring in such cells, but if the increased cell loss indicates an increase in the recombinase error rate, as has been suggested, then the risk of developing a genetic abnormality may be greater than would be suggested by the increase in precursor cell numbers alone. Moreover, the stage specificity of the effects of an environmental agent may be important both with regard to the fragility of various regions of the involved genetic loci (because of different patterns of proteins bound to the DNA of these regions) and with respect to the functional consequences (on c-myc transcription) of the breakpoint locations. Cells at different stages of differentiation, for example, may express different protein factors relevant to c-myc or immunoglobulin regulation.

**EBV Can Cooperate with the c-myc/Immunoglobulin Translocation.** Recently, we have been able to demonstrate that one of the EBV latent genes (i.e., genes expressed only in the non-replicative phase of EBV infection), EBNA1, can collaborate with the chromosomal translocation (66) in affecting the transcription of c-myc, and it seems likely that in some circumstances the presence of EBV is essential to the deregulation of c-myc. Factors which influence the number of EBV-containing cells in the body and the rate of infection of cells which have the potential to undergo transformation into tumor cells (e.g., immature B-cells in the bone marrow, particularly the bone marrow of the jaw in African children) probably influence the risk of the development of Burkitt’s lymphoma. Factors that have been shown to increase the level of EBV-infected B-cells in peripheral blood by impairing EBV-specific immunity include malaria (or inherited or acquired immunosuppression, including AIDS), while phorbol esters, derived from a plant, *Euphorbia tirucalli*, widely used for medicinal purposes in Africa, appear able to increase the efficiency of infection of EBV as well as to increase the likelihood of translocations (67, 68). Malaria and *Euphorbia* in combination, therefore, may increase the levels of specific B-cell precursors in bone marrow, increase the likelihood that they will be infected by EBV, and perhaps also increase the risk of a genetic error. The additive effect of these effects may well be enough to explain the greatly increased frequency of a particular molecular subtype of EBV-associated Burkitt’s lymphoma in equatorial Africa. The early age of EBV infection (100% by 3 years of age) in Africa presumably also contributes to the epidemiological picture.

In other world regions there is no evidence that climatic factors influence distribution, but environmental agents not encountered in Africa, possibly other infectious agents, may still influence the frequency of EBV-associated Burkitt’s lymphoma as well as the overall incidence of the tumor and the chromosomal breakpoint locations in any given geographical region. Interestingly, EBV can be associated with all molecular subtypes of Burkitt’s lymphoma (60, 64), suggesting that cooperation with myc/immunoglobulin translocations does not involve a direct interaction with c-myc regulatory elements.

**Other Genetic Lesions.** There is experimental evidence from mice transgenic for c-myc that, although the myc/immunoglobulin translocations can lead to continued proliferation of precursor B-cells, such that they do not enter a resting phase as they differentiate, additional genetic lesions (which can substitute for each other) are required to generate a neoplasm (69, 70). The infrequency of occurrence of these additional lesions presumably accounts for the monoclonality of the resultant tumors. In Burkitt’s lymphoma, several genetic abnormalities in addition to the c-myc/immunoglobulin translocations have been identified, the most prominent being p53 mutations that occur in some 30% of freshly biopsied tumors (49, 50). Occasional ras and Rb mutations have also been observed (71). No correlations between these additional genetic lesions and geographical origin, the presence or absence of EBV, or the chromosomal breakpoint location have been discerned to date, and it appears that a number of alternative lesions may be able to contribute to pathogenesis, as is the case in *Eµ-myc* transgenic mice (69, 70). One of these is presumably able to substitute for EBV in EBV-negative tumors.

**Hypothesis**

These observations can be assembled into a hypothesis to account for the environmental interactions that determine the incidence of Burkitt’s lymphoma. While it is highly probable that several genetic lesions are necessary to induce the neoplasm, a central requirement is myc deregulation. This is accomplished by the myc/immunoglobulin translocations which occur early in B-cell differentiation. The functional result of deregulated myc expression is maintenance of the cell in a perpetually proliferative state, even though it can mature to the stage of an immunoglobulin-expressing and even secreting cell. The perpetual proliferation of cells bearing a translocation, and presumably the expansion of the cell clone, increases the likelihood of the development of additional genetic abnormalities, although it appears that the nature of these additional lesions varies from one tumor to another, suggesting that several different mutations are able to interact with the chromosomal translocation during oncogenesis. EBV can also cooperate with the translocation, and whether or not it is an absolute requirement is probably dependent upon either the specific stage of precursor cell in which the translocation occurs or perhaps the presence or absence of other, environmentally determined genetic lesions. Factors that increase the numbers of circulating EBV-infected cells (which may thus affect the number of B-cell precursors infected with EBV), including malaria, AIDS, and perhaps early age of EBV infection increase the risk of the development of EBV-associated Burkitt’s lymphoma. Finally, the likelihood that a translocation will occur is dependent upon the number of potential target cells present in an individual, a factor that is influenced by age, the environment, and life-style, while the relative proportions of cells at different levels of differentiation probably influence the molecular characteristics (chromosomal breakpoints) of the translocation.
Clearly major strides have been made in recent years in understanding the pathogenesis of lymphomas at a molecular level. It is to be hoped that this new information, and information yet to come, will be of practical as well as theoretical value, i.e., that it will lead to improved diagnosis and classification, to measures designed to prevent the continuing increase in the incidence of non-Hodgkin's lymphomas and, perhaps also, to new approaches to treatment.

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