REVIEW ARTICLE

Gene Rearrangements and Translocations in Lymphoproliferative Diseases

By Henrik Griesser, Douglas Tkachuk, Marciano D. Reis, and Tak W. Mak

LYMPHOID LEUKEMIAS and malignant lymphomas are neoplasms characterized by the proliferation of cells derived from the lymphoid tissue and its precursors. Like other malignant hematological disorders, the majority of these lymphoid malignancies are of monoclonal origin. Although clonality does not necessarily correlate with a clinically malignant course of disease, the detection of a clonal population of proliferating cells may help in the discrimination between a reactive process and an autonomous, preneoplastic, or neoplastic lesion. The determination of B- or T-cell lineage in these malignant lymphoproliferative disorders has clinical significance. When compared with patients having B-cell malignancies, patients with T-cell malignancies, other than mycosis fungoides, generally tend to have a more aggressive clinical course and poorer response to therapy. As an example, cases of T-cell chronic lymphocytic leukemia (T-CLL) with a helper phenotype (CD4+), or rarer cases of cytotoxic (CD8+) T-CLL have a poorer prognosis than B-CLL cases. However, intensified treatment regimens have led to improved remission duration, especially in T-cell acute lymphoblastic leukemia (T-ALL), where statistically significant differences cannot be demonstrated between the total ALL group and aggressively treated T-ALLs. Large clinical trials comparing prognosis of uniformly staged and treated patients with T-cell diffuse large-cell lymphomas and comparable histologic subtypes of B-cell lymphomas are required to ascertain the significance of lymphoma lineage.

Over the past several years, the increasing availability of highly specific monoclonal antibodies has made it possible to clearly define the lineage and stage of differentiation of a large number of malignant lymphoproliferative disorders. Most non-T ALL and mature B cell non-Hodgkin’s lymphomas can be classified using panels of lymphoid-associate markers, which delineate stages of lymphoid differentiation, and antibodies against μ and λ immunoglobulin light chains (IgL), which define clonality, in addition to and combined with the more traditional morphologic analysis. However, if the malignant B cells constitute only a small minority of cells in a lymphoid tumor with abundant reactive B or T cells, restriction of IgL surface expression may not be detectable. Especially in non-T non-B–cell ALL and T-cell disorders, clonality cannot be determined by analysis of surface proteins. The study of many T-cell–rich lymphoproliferative diseases, such as T-cell leukemia and lymphoma, lymphoepithelioid (Lennert’s) lymphoma, large cell anaplastic lymphomas with the activation-associated antigen Ki-1 (CD30+), and a large proportion of cases of angioimmunoblastic lymphadenopathy (AILD), has remained difficult. For certain malignant disorders, such as the non-T non-B ALLs and large cell anaplastic CD30+ lymphomas, it has not been possible to assign lineage with monoclonal antibodies. In Hodgkin’s disease (HD), immunophenotyping and other conventional methods have failed to clearly characterize a clonal cell population or define lineage of the malignant cells.

With the availability of molecular probes for human immunoglobulin (Ig) and T-cell receptor (TcR) genes, the clonality and lineage of certain putative B- or T-cell malignancies can now be investigated by gene rearrangement studies. This approach has been used successfully to distinguish monoclonal from polyclonal lymphoid proliferations, and to determine the lymphocytic lineage of neoplasms lacking lineage-specific surface determinants. Furthermore, the high sensitivity of this method allows the detection of circulating monoclonal lymphoid populations that constitute only 1% of the mononuclear blood cells, even in the absence of any other evidence of disease. Especially with the TcR gene probes, a diagnostic tool is available that, combined with morphological and immunocytochemical analyses, potentially helps in the classification of monoclonal T-cell proliferations according to their developmental stage. Similar to the hierarchical sequence of TcR gene activation documented in murine thymocytes, it has been found in human T-cell leukemias that TcR γ and TcR δ rearrangements occur early together with the surface expression of the CD7 antigen, and CD2 antigen expression is detectable when TcR β rearranges. TcR α genes are fully transcribed in T cells with surface expression of CD3, CD4, or CD8 antigens. In most situations, the types of gene rearrangements are indicative of the lineage involved. For example, the rearrangement of TcR β chain genes without Ig gene rearrangement strongly supports a T-lineage. On the other hand, rearrangements of immunoglobulin heavy chain (IgH) with or without Ig light chain genes, without alteration of the germline TcR β chain genes, imply B-cell origin of the neoplasm.

With the use of Ig and TcR gene probes, many groups have also examined several chromosomal translocations occurring in lymphoproliferative disorders. Detailed analyses of the breakpoints showed either of these genes to be involved, sometimes with protooncogenes, in these translocations.

In the last several years, many laboratories have per-
formed detailed genotypic analyses of a large number of various types of lymphoproliferative disorders using probes for the TcR α, TcR β, TcR γ, and TcR δ, IgH, Igκ, and Igλ chain genes. A summary of these studies is presented in Table 1. In general, the rearrangement of Ig and TcR genes has correlated with malignancies of B- and T-cell origins, respectively. However, in a minority of cases, not only TcR but also Ig gene rearrangements have been shown to occur in the same tissues or cell populations. These findings have shown that in some neoplasms, particularly the immature B-cell and nonlymphoid malignancies, immunogenotyping fails to conclusively and correctly define lineage, and immunophenotyping is required. For example, concurrent rearrangement of TcR and Ig genes has frequently been seen in non-T non-B–ALL and in a few cases of acute myeloid leukemia (AML).37,38

In this review, we summarize and discuss Ig and TcR gene rearrangements in lymphoproliferative disorders. We propose that the complexity of rearrangement patterns is not necessarily arbitrary, but may reflect a clonal cell population arising from an undifferentiated hematopoietic cell that is capable of Ig and/or TcR gene rearrangements prior to the acquisition of T- or B-cell lineage characteristics. This is suggested by the observation that, in some instances, morphologically distinct lymphoma entities have a characteristic pattern of Ig and TcR gene rearrangements, indicating that they correctly identify the lineage of these lymphoproliferative disorders. Also, we will briefly discuss the chromosomal translocations found in some lymphoid neoplasms involving the Ig or TcR genes.

**GENES OF IMMUNOGLOBULIN AND THE T-CELL RECEPTORS**

The immunoglobulin molecules consist of a pair of two identical heavy (IgH) chains and two identical light (IgL) chains. There are two types of heterodimeric T-cell antigen receptors, one containing an α and a β chain (the first type to be described), and a second consisting of a γ-δ heterodimer.14,15,40,41

The chromosomal location and genomic organization of the genes encoding the Ig and TcR polypeptides is known.10,11,39,40,42-45 These genes are arranged in their germ-

### Table 1. T-Cell Receptors and Immunoglobulin Gene Rearrangements in Lymphoproliferative Diseases

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The configurations of the T-cell receptors (TcR) and immunoglobulin (Ig) genes in cells from a variety of lymphoproliferative diseases are summarized. Germline (G) and rearranged (R) structures of these genes are denoted. The distributions of the individual types of disorders with a specific pattern of rearrangement are expressed as frequency of the total number of cases examined, highest to lowest percentages are denoted as ++++, +++, ++, +, and 0, respectively. Data compiled from a survey of the literature including references 2, 12-39, 44, 46, 47, 56, 58, 63-69, 73-89, 94-96, and 149-169.

Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; B-ALL, B cell acute lymphoblastic leukemia; non-T non-B, common acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; ATL, adult T-cell leukemia; Kil* (CD30), anaplastic large lymphoma positive for the surface antigen Kil (CD30); AILD, angioimmunoblastic lymphadenopathy; NT, not tested.

*Patterns most likely representing only DJ rearrangements.
†Analyses included both rearrangement and deletion of the δ chain genes.
‡Data based on analysis of 12 patient samples.
line configuration as discontinuous segments of DNA (Fig 1), and contain coding segments termed variable (V), diversity (D, in the case of IgH, TcR \( \beta \), and \( \delta \) genes), joining (J) and constant (C) region genes of Ig and TcR molecules. The immunoglobulin genes IgH, IgA, and IgGx are located at chromosomes 14q32, 22q11, and 2p11, respectively. The TcR \( \alpha \), TcR \( \beta \), and TcR \( \gamma \) are situated at 14q11, 7q34, and 7p13, respectively (Fig 1).

As a mandatory step in B- and T-cell lineage commitment, the Ig and TcR genes undergo somatic rearrangements. There is an orderly sequence of events that may ultimately lead to a functional rearrangement with transcription of a complete or functional Ig or TcR messenger RNA. Initially, a D gene segment (in IgH and TcR \( \beta \)) combines with any one of a J segment (partial rearrangement: step 1, Fig 2). Then this DJ segment combines with a V gene segment (complete rearrangement: step 2, Fig 2), thus forming a variable region gene assembly, which together with a constant region gene, constitutes a completely rearranged Ig or TcR gene.40,41,39,42-45 (Fig 2).

It has been demonstrated that during normal B- and T-cell differentiation and in precursor B-cell lines, the IgH is the first locus to undergo rearrangement that, if successful, results in a \( \mu \) cytoplasmic heavy chain being synthesized.46

Next, there is an attempt at a light chain gene rearrangement that, if productive, results in a \( \mu \)-Ig being produced.44 If no productive \( \kappa \) rearrangement occurs, the cell next tries to rearrange the \( \lambda \) chain genes. If functional (resulting in a translational open reading frame), rearrangement leads to the production of an \( \mu \), \( \kappa \) polypeptide; if inefficient or aberrant (nonfunctional open reading frame), there is no synthesis of light chains and the cell remains at the pre-B stage.247

The exact hierarchy of TcR gene activation is not entirely known, although it has been demonstrated that TcR \( \gamma \) chain gene rearrangement precedes that of TcR \( \beta \) genes,46,49 and that the TcR \( \alpha \) gene is the last to rearrange. The timing of TcR \( \delta \) gene activation relative to the other TcR genes is still uncertain, but it is possible that it occurs at about the same time as the rearrangement of the TcR \( \gamma \) genes.33

These rearrangement events can result in the generation of a vast repertoire of antigen receptors (Ig and TcR molecules) of unique specificities.40,11,39,43,44 In addition to the multiple germline Ig and TcR V, (D), and J segments and their random combinatorial possibilities, there is junctional flexibility at the joining sites of the V, D, and J gene segments,50 and the template-independent insertion of one to a couple of dozen nucleotides at the ends of the junction of the Ig and TcR gene segments (N insertion), regulated by the enzyme terminal deoxynucleotidyl transferase (TdT).51,52 An extra mechanism for generation of antibody diversity is somatic hypermutation, occurring in genes encoding the variable region of Ig polypeptides, resulting in an antibody of higher affinity for the antigen against which it is directed.53,54 A similar mechanism has not been documented for TcR genes thus far.

**IMMUNOGENOTYPIC ANALYSIS OF LYMPHOPROLIFERATIVE DISORDERS**

A phenomenon of great biological importance and practical diagnostic implications is that each individual B or T cell produces an antigen receptor consisting of a combination of two (IgH and IgL, TcR \( \alpha \) and TcR \( \beta \), or TcR \( \gamma \) and TcR \( \delta \)) variable region sequences of unique specificity. The progeny of these individual cells will have receptors with the same characteristics of those of the parent cells. Thus, for example, a mature B cell and its progeny will exhibit the same variable region sequences at the Ig gene and polypeptide level, except for possible variation resulting from somatic hypermutation, and will produce either \( \kappa \) or \( \lambda \) light chains, but not both.46,11 This Ig light-chain restriction present in clonal populations can be detected by immunological studies. An even more powerful tool for the detection of clonal lymphoid population is DNA analysis, exploiting the fact that cells from a clonal population exhibit the same gene rearrangement pattern. This modality of analysis allows not only the detection of

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**Fig 1.** Germline genomic organizations and chromosomal locations of the human immunoglobulin genes IgH, IgA, IgGx, and the T-cell receptor genes \( \alpha \), \( \beta \), \( \gamma \), and \( \delta \). V, variable; D, diversity; J, joining segments; C, constant region genes. The gene organizations are reconstructed from references 10, 11, 14, 39, 40, 42, 43, 60, and 62.
clonality and, in most instances, the assignment of cell lineage, but also the documentation of extension of lymphoproliferative disorders to different sites of involvement, or the presence of residual disease following therapy. For this purpose, DNA from affected cells is digested with restriction endonuclease, size-fractionated by agarose gel electrophoresis and then transferred to nitrocellulose paper according to the Southern procedure. Hybridization to radioactive-labeled DNA probes for Ig or TcR genes is followed by autoradiography. If more than 1% to 5% of a given cell population contain the same rearrangement, a new band different from the rearranged germline band(s) is detectable with the use of current techniques routinely used. However, in a heterogeneous population of lymphocytes, the Southern blot will not show new distinct bands but a vertical smudge indicative of a polyclonal population. Contained within the smudge are DNA fragments reflecting numerous rearrangement patterns, none of which predominates in a polyclonal population. Examples using a TcR β probe in the analysis of DNAs from a non-neoplastic mixed population of T lymphocytes, a lymph node from a patient with T-cell lymphoma, clonal T cells from a patient with T-ALL, and nonlymphoid cells (granulocytes) showing a control germline configuration of the gene are illustrated in Fig 3 (lanes 1, 2, 3, and 4, respectively).

Many attempts at optimizing the conditions for cell preparation and DNA analysis have been undertaken. It has been reported that minor leukemic population, as little as 0.15%, could be detected in bone marrow samples of patients considered to be, by morphologic analysis, in apparent complete remission. Another technique that has produced remarkable results in the investigation of residual hematologic malignancies is the amplification of certain DNA sequences by the polymerase chain reaction (PCR). This requires that the sequence of a segment of DNA flanking the area of interest be known. The PCR technique has been used to amplify nucleic acid sequences flanking the chromosomal

**Fig 2.** Two examples depicting the sequential rearrangement of (1) D to J (partial rearrangement), and (2) V to DJ (complete rearrangement) of the human T-cell receptor β chain genes. At the DNA level, J segments 5' (upstream) from the J segment and V gene segments 3' (downstream) of the V segment involved in V-J rearrangements are deleted. Due to RNA-splicing, the downstream J segments will not be present in the messenger RNA molecules.

**Fig 3.** Southern gel analysis of DNAs from (1) mixed population of human T lymphocytes (rearranged, polyclonal); (2) T-cell lymphoma (rearranged, clonal); (3) T cell leukemia (rearranged, clonal); and (4) granulocytes (germline configuration, unrearranged).
breakpoint involved in a case of follicular lymphoma, with the t(14;18) translocation unique to the neoplastic cells. This has allowed the detection of the t(14;18) lymphoid sequences at a 1:100,000 cell dilution ratio, and in bone marrow specimens from the same case, considered incomplete clinical remission.37

Molecular analyses of Ig gene rearrangements have aided in the investigation of important clinical problems. Studies in which Ig gene probes were used in conjunction with immunophenotypic analysis of then so-called null-cell–ALL showed that the great majority of these cases had their Ig heavy chain, and in some cases the Ig light chain genes, rearranged.38 These non-T, non-B leukemias have then been assigned to B-lymphoid lineage, and the predicted pattern of light chain rearrangement preceding light chain rearrangements was confirmed.39 Furthermore, similar studies have allowed the schematization of the relationship between the orderly rearrangement and expression of Ig genes in synchrony with the expression of B-lymphocyte–associated differentiation antigens at the various stages of B-cell ontogeny.39 Since the occurrence of IgH chain gene rearrangement has been observed in non-B cells, it is insufficient for the assignment of B-lymphoid origin, whereas the presence of IgL chain rearrangement is considered B-lineage–specific.

TcR AND Ig REARRANGEMENTS AS MARKERS FOR CLONALITY

In the vast majority of lymphoproliferative neoplasms, including all cases of AILD and some samples of HD, the presence of clonal lymphoid populations can be demonstrated using TcR and Ig gene probes (Table 1).2,12,34,39,44,46,47,56,58 Many of these diseases consistently show characteristic patterns of rearrangements. For example, T-cell lymphomas, T-cell leukemias, and T-cell lymphoma cell lines almost always have clonally rearranged TcR γ and β chain genes (and, in some cases, TcR δ chain genes),32,33 without rearrangement of Ig genes. These findings are expected from what is known about the morphology and immunocytochemistry of these lymphoproliferative neoplasms. The knowledge about TcR α gene rearrangements in T-cell malignancies is still limited because of the physical structure of this gene (Fig 1). A macrorestriction mapping of human genomic DNA, by means of pulse field electroporesis, has shown that the entire TcR α-δ locus spans close to 1,000 kilobase (kb) pairs.40 The V α-δ genes are spread out over 750 kb,40 and a large number of Jα segments, estimated at >100,39,41 are dispersed over approximately 80 kb upstream from the only Cα gene. This probably explains the difficulty encountered initially in demonstrating rearrangement of TcR α genes with the probes then available. However, more recent studies employing a few Jα gene probes have documented TcR α gene rearrangement in lymphoproliferative disorders.30,33,40,60

With the availability of genomic DNA probes, which cover the entire J locus,43 more knowledge about TcR α gene rearrangements in lymphoid neoplasms will be accumulated in the near future.

Clonal rearrangements of TcR genes (γ, β, and δ), and not Ig genes, have been detected in different cases of Lennert’s lymphoma, providing further evidence that this is a T-cell lymphoma with special immunocytochemical and morphological characteristics.27,28,32,33,34 The results seen in HD are more controversial.44–70 Some laboratories have reported that in a proportion of HD, a small but significant population of clonal cells have rearranged TcR γ and/or TcR β chain genes. In cases containing high numbers of Reed-Sternberg (RS) cells, either TcR γ or IgH rearrangements were found.45–70 Similarly, Ig gene rearrangements have been found in three of five cases in which RS cells and their variants were enriched by cell separation techniques.45 Recently, functional TcR α transcripts have been demonstrated in the Hodgkin’s-derived cell line L450,64, and in the cell line L428, IgH, IgL, and TcR β genes have been found to be rearranged.63 The rearranged bands, detected in most cases of HD with Ig and TcR gene probes, are mostly of lower intensity than in non-Hodgkin’s lymphomas and represent only minor cell populations. The occasional detection of an intense rearranged band in HD tissue64,65 argues against the claim that immunogenotypic analysis is an accurate and objective tool in the differential diagnosis between Hodgkin’s and non-Hodgkin’s lymphoid neoplasia.37 More likely, the rearrangement results suggest a relationship between these two entities, at least in some of the cases. Further investigations are needed to substantiate these findings. In particular, the finding of exclusive TcR γ rearrangement needs to be evaluated.

It has been recently demonstrated that the TcR γ chain is part of a γ-δ heterodimer on the surface of CD3+, sometimes CD8+, and mostly CD4+ lymphocytes.46 The TcR δ genes have been characterized in humans.15,40,71 Although the function of the γ-δ heterodimer is not yet fully understood,46 the location of the δ chain gene locus is particularly interesting. The human TcR δ C region40,46 gene is located 85 kb upstream of the TcR α C region gene,15 and just 5’ to the more than 100 Jδ gene segments43,60,62 (Fig 1). Three Jδ and three Dδ genes have been identified,40 and rearrangement of these gene segments has been shown in TcR δ-expressing cell lines.15,71 TcR δ rearrangement has been found in a significant proportion of T-ALL33 and T-cell lymphomas,32 and less often in cases of B-cell lymphomas,32 precursor-B ALL,31 B-cell leukemia lines,32 AILD,32 Lennert’s lymphoma,32 and CD30+ lymphomas.32 Although a high proportion of these rearrangements at the TcR δ and TcR α loci is a result of true rearrangement of these genes, some of these changes may reflect chromosomal translocations at these loci (see below). In one series, TcR δ gene rearrangement was always seen with concurrent rearrangement of TcR γ and β genes.32,33

The existence of two separate centers (α and δ) of rearrangement, within one locus (chromosome 14q11), that are involved in rearrangement events at different times during ontogeny, and the presence of high number of J segments in this region9,40,41,60,62 may render the locus highly vulnerable to chromosomal translocations during T-cell development. This could account for recurrent chromosomal aberrations involving the 14q 11-13 region, commonly seen in T-cell malignancies (see below).

In summary, TcR gene rearrangement studies can define clonality and, due to the sensitivity of these techniques,19,20
help to identify early relapse or minimal residual disease during clinical remission. In the same manner, clonal rearrangements of TcR genes (γ, β, and δ), and not Ig genes, have been detected in different cases of Lennert's lymphoma, providing further evidence that this is a T-cell lymphoma with special immunocytochemical and morphological characteristics. The results with HD are more controversial. Some laboratories have reported that in a proportion of HD, a small but significant population of clonal cells have rearrangement in either TcR γ and/or TcR β chain genes.

DOES MONOCLONALITY NECESSARILY IMPLY MALIGNANCY?

In cases of B-cell lymphomas and B-cell leukemias, the IgH and, in some cases, IgL chain genes are rearranged. This confirms the B-cell origin of these neoplasms. By this means, hairy cell leukemia has been shown to represent a mature B-cell malignancy. However, it has to be kept in mind that the detection of clonal rearrangement by itself does not necessarily imply a malignant course of disease. Monoclonality was found not only in T8 lymphocytosis, where “classical” cases with CD8 lymphocytosis and neutropenia all had clonal TcR γ and β gene rearrangements, but also in benign lymphoproliferative diseases with increased susceptibility to the development of non-Hodgkin’s lymphoma, and in CD3+ large granular lymphocytic leukemia. Clonal TcR and/or Ig gene rearrangements have also been documented in various lymphoid disorders, or different clonal immunodeficient or immunosuppressed patients revealed oligoclonality in the same tumor (as demonstrated in AIDS-related lymphoproliferative disorders), or different clonal rearrangement patterns in tissues taken from different sites or at various times (as shown in transplant recipients with lymphoproliferations). These findings provide insights into lymphomagenesis. There is some evidence that oligo- clonal lymphoproliferations, probably virally induced, emerge on the background of congenital or acquired immunodeficiency. Eventually one of these clones predominates and a clonal rearrangement becomes detectable, but as yet no malignant course of disease is evident and spontaneous regression may occur. At least one more event (such as chromosomal translocations involving regulatory genes or a total breakdown of the immune system) must occur, resulting in malignant transformation. Thus, although the establishment of a monoclonal population is associated with and may be a prerequisite to neoplastic growth, its presence does not obligatorily imply malignancy.

CROSS-LINEAGE REARRANGEMENTS OF TcR AND IG GENES

Results presented in Table 1 show that unlike B-CLL, where only few cases with TcR β rearrangement have been reported, a considerable proportion of non–T non–B-cell acute lymphoblastic leukemias, and fewer of B-cell lymphomas, also have rearranged some of their TcR genes (especially the TcR γ and TcR δ), in addition to their Ig genes. This suggests that rearrangement of the TcR γ and TcR δ genes may serve as a marker of clonality, but is not an accurate indicator of T-cell lineage. However, due to the limited number of V, D, and J gene segments in TcR γ and δ weak but visible rearranged bands can be observed in some polyclonal T-cell populations. The TcR β, δ, and α chains rarely show complete rearrangement (VDJ in TcR β, VDJ in TcR δ, and VJ in TcR α) in B-cell leukemias or lymphomas. On the other hand, very few cases of T-ALL or T-CLL (A. Aisenberg, personal communication, February 1989) have been reported where the cells have rearranged their IgH genes in addition to the expected rearrangement of their TcR genes. In fact, it is very rare that B-CLL and T-CLL (A. Aisenberg, personal communication, February 1989) have rearrangements of either their TcR or Ig genes, respectively.

One explanation for Ig and TcR gene rearrangements in the same leukemia or lymphoma sample may be the presence of clonal populations of both T and B cells. However, it is unlikely because the neoplastic cells in B-cell leukemias have immunocytochemical features of B cells. Furthermore, genotypic analyses of lymphomatous lesions in immunodeficient or immunosuppressed patients revealed oligoclonality in the same tumor (as demonstrated in AIDS-related lymphoproliferative disorders), or different clonal rearrangement patterns in tissues taken from different sites or at various times (as shown in transplant recipients with lymphoproliferations). These findings provide insights into lymphomagenesis. There is some evidence that oligo- clonal lymphoproliferations, probably virally induced, emerge on the background of congenital or acquired immunodeficiency. Eventually one of these clones predominates and a clonal rearrangement becomes detectable, but as yet no malignant course of disease is evident and spontaneous regression may occur. At least one more event (such as chromosomal translocations involving regulatory genes or a total breakdown of the immune system) must occur, resulting in malignant transformation. Thus, although the establishment of a monoclonal population is associated with and may be a prerequisite to neoplastic growth, its presence does not obligatorily imply malignancy.
TcR gene rearrangements in certain cases of AML supports this hypothesis. It is intriguing that a high frequency of unexpected IgH and/or TcR β gene rearrangements (about 50%) was found in cases of TdT+ AML, as opposed to a much lower frequency (about 10%) of rearrangement of these genes in TdT-AML.

The frequency of rearrangements of both TcR and Ig genes is substantially higher in lymphoproliferative disorders in which T- or B-cell lineage is uncertain on the basis of historical and immunological analyses. These include non-T non-B-ALL, AILD/AILD-like lymphomas, and large cell anaplastic CD30+ lymphomas. Samples from CD30+ lymphomas and AILD often contain tumor cells with rearrangement of both IgH and TcR genes. In the majority of these situations, the TcR γ genes are more frequently rearranged than the TcR β and δ genes. However, cells with TcR γ rearrangement only display no apparent bias toward rearrangements of either their IgH or TcR β chain genes. The malignant cell in these disorders seems to be derived from immature lymphoid cells with incomplete rearrangements at a stage of differentiation prior to lineage commitment. In some cases of CD30+ lymphomas and most cases of AILD, rearrangement of the TcR γ, β, and δ chain genes has occurred, while both the IgH and IgL genes remain in germline configuration, suggesting that these tumors are probably mostly of T-cell origin. In most of these cases, these findings are confirmed by immunocytochemical studies.

Perhaps the most heterogeneous group of lymphoproliferative diseases with regard to immunogenotype is that of non-T, non-B, or precursor B-ALL. A large proportion of these leukemias have undergone clonal rearrangement of not only the IgH, but also of the TcR β, TcR α, and/or TcR γ chain genes with or without TcR β rearrangement. The malignant cell population expresses only cytoplasmic Ig μ chains. These observations may suggest that the malignant clone in those cases was derived from an early lymphopoietic cell in which deregulation of hierarchical, lineage-specific, and recombinational events has occurred.

Although extensive studies have revealed a complexity of rearrangement patterns, the patterns involved at multiple gene loci are probably related in most cases to the nature of the clonal cell populations involved in these disorders, and may reflect the stage of differentiation from which these clones emerge. The very low incidence of TcR and Ig rearrangement in the more mature B-CLL and T-CLL (A. Aisenberg, personal communication, February 1989), respectively, supports this hypothesis. A minor proportion of these rearrangements may also reflect chromosomal translocations at these loci (see below).

TRANSLOCATIONS INVOLVING THE TcR AND Ig GENES IN LYMPHOPROLIFERATIVE DISORDERS

Recurrent specific chromosomal abnormalities have been documented in some hematological neoplasias. The first to be observed was the Philadelphia chromosome seen in most cases of chronic myeloid leukemia (CML), and later shown to involve a translocation between chromosomes 9 and 22, t(9;22) (q24;q11). This results in the proto-oncogene c-abl being translocated from chromosome 9 to chromosome 22 at band q11 and fusing to breakpoints occurring within a short segment of DNA on chromosome 22 called bcr. This fused gene results in an aberrant hybrid c-abl-bcr RNA translated into an abnormal protein with protein kinase activity, thought to play a role in malignant transformation.

Some translocations have been seen in lymphoproliferative disorders (Table 2). A marker 14q+ chromosome was first detected in Burkitt’s lymphoma and is now known to represent any of three variant reciprocal translocations involving the c-myc proto-oncogene, normally located on chromosome 8, and the loci for IgH, Igα, or Igλ, mapped to chromosomes 14, 2, and 22, respectively. The t(8;14) (q24;q32) is the most common of these translocations, seen in approximately 75% of Burkitt’s lymphomas. The normal c-myc proto-oncogene on the normal chromosome 8 is not transcribed, whereas the c-myc gene involved in each of the three distinct chromosomal translocations is constitutionally transcribed at elevated levels. The location of the breakpoints in the c-myc and Ig genes has been determined, and it is postulated that the deregulation of transcription of c-myc is involved in the pathogenesis of Burkitt’s lymphoma.

The t(11;14) (q13;q32) chromosome translocation is seen in CLL. This diffuse B-cell lymphomas and multiple myeloma. The translocation splits the IgH locus and a locus termed bcl-1 (B-cell lymphoma/leukemia 1) was identified by cloning the breakpoint between chromosomes 11 and 14.

The t(14;18) (q32;q21) seen in most follicular lymphomas involves one of the JH segments of the IgH locus on chromosome 14 and a gene called bcl-2, whose deregulation is considered to be involved in the pathogenesis of this type of human lymphoma. Studies suggest that the t(11;14) and the t(14;18) translocations occur during the process of V-D-J joining, with signal sequences recognized by the enzyme catalyzing VDJ joining present near the breakpoints on chromosomes 11 and 14.

Recurrent chromosomal abnormalities have also been described for T-cell disorders, involving any of the TcR chain genes, but predominantly affecting the 14q 11-12 region, where the TcR α and δ loci are located. Examples of chromosomal abnormalities affecting this region are the reciprocal translocations t(8;14) (q24;q12) and t(11;14) (q13;q21) and t(10;14) (q24;q11), plus the inversion inv(14) (q11;q32).

In the t(8;14) (q24;q12), the breakpoint involves the...
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Table 2. Translocations Involving TcR and Ig Genes in Lymphoproliferative Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Translocation</th>
<th>Loci Involved</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt’s lymphoma/leukemia</td>
<td>t(8;14)(q24;q32)</td>
<td>c-myc-lgH</td>
<td>103-106</td>
</tr>
<tr>
<td>B-cell follicular lymphoma</td>
<td>t(11;14)(q13;q32)</td>
<td>TcR-y-lgH</td>
<td>105-110</td>
</tr>
<tr>
<td>B-CLL, MM, B-cell diffuse lymphoma</td>
<td>inv(14)(q11;q32)</td>
<td>c-myc-lgH</td>
<td>115, 116, 135</td>
</tr>
<tr>
<td>Pre-T or T-cell leukemia/lymphoma</td>
<td>t(8;14)(q24;q11)</td>
<td>TcR-y-lgH, IgH-bcl-2</td>
<td>112-116</td>
</tr>
<tr>
<td></td>
<td>t(10;14)(q23;q11)</td>
<td>c-myc-lgH</td>
<td>117-120, 127, 140</td>
</tr>
<tr>
<td></td>
<td>t(11;14)(p13;q11)</td>
<td>onc-r-TcR</td>
<td>121, 122, 130</td>
</tr>
<tr>
<td></td>
<td>t(11;14)(p15;q11)</td>
<td>onc-r-TcR</td>
<td>118-120, 128, 129</td>
</tr>
<tr>
<td></td>
<td>inv(14)(q11;q32)</td>
<td>lgH-TcR</td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>t(17;14)(q11;q32)</td>
<td>lgH-TcR</td>
<td>119, 123-126, 132, 133, 135, 136</td>
</tr>
<tr>
<td>Ataxia-telangiectasia and/or activated T cells</td>
<td>inv(7)(p15;q33)</td>
<td>TcR-r, TcR-y</td>
<td>132, 141</td>
</tr>
<tr>
<td></td>
<td>t(7;9)(q34;q33)</td>
<td>TcR-y-lgH</td>
<td>132, 142</td>
</tr>
<tr>
<td></td>
<td>t(1;14)(p32;q11)</td>
<td>L-myc-lgH, N-ras-lgH</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>src-lgH</td>
<td>src-7-lgH</td>
<td>128-139, 144-146</td>
</tr>
</tbody>
</table>

region containing the J_a segments and results in the C_a being gene translocated to a region immediately 3' of the c-myc proto-oncogene. It is postulated that the c-myc gene is activated in a manner analogous to its activation in Burkitt’s lymphoma. The exact nature of a possible gene located in the p13 region of chromosome 11 and involved in the t(11;14) (p13;q11) is not known. This locus has been implicated in the development of Wilms’ tumor, and it is possible that a yet-unidentified gene may be involved in tumorigenesis as a result of its altered structure or expression, associated with the translocation into the TcR_y chain locus. In several cases of T-ALL with the t(11;14) (p13;q11) translocation, cloning and sequencing of the breakpoint on chromosome 14 revealed the TcR_y locus to be involved in the translocation. The t(10;14) (q24;q11) has been observed in cases of T-ALL and high-grade T-cell lymphoma. In one study, the breakpoint on chromosome 10 was found to be distal to the TdT gene. The C_a gene was translocated to chromosome 10 and the V_a region remained on the 14q+ chromosome. It has been suggested that a putative proto-oncogene, called TCL3, is located proximal to the breakpoint at 10q24. Another translocation t(11;14) (p15,q11), in T-cell line RPMI 8402, with the breakpoint at the T-cell receptor 6 chain locus has also been analyzed. This translocation may involve another proto-oncogene.

Finally, the inv(14) (q11;q32) has been found not only in T-cell neoplasms (such as T-cell lymphomas and T-CLL) but also in monoclonal T-cell leukemias; but also in monoclonal T-cell populations, seen in patients with ataxia-telangiectasia and in B cells. Two breakpoints have been documented on the long arm of the inverted chromosome 14. The telomeric breakpoint is involved in the formation of a fused structure in which a proto-oncogene is not known to be involved in the inversions.

Translocations between chromosomes 7 and 14 as well as inv(14) (q11; q32) have been seen occasionally in stimulated normal T cells and in T cells from patients with ataxia-telangiectasia.

CONCLUSION AND PERSPECTIVES

Rearrangement studies using Ig and TcR gene probes are useful for the detection of clonal cell populations in lymphoproliferative diseases, and in association with the clinical course, help to distinguish reactive lymphoid conditions from malignant clonal proliferations. The use of these probes, in association with immunocytochemistry, should allow the assignment of most, if not all, of the clonal lymphoid proliferations. The use of these probes, in association with immunocytochemistry, should allow the assignment of most, if not all, of the clonal lymphoid disorders to the T- or B-cell lineage, and may also provide information about the possible stage of differentiation from which the tumor cell clones emerge. These molecular probes are especially useful for the analyses of lymphoid malignancies in which monoclonal antibodies against surface markers are unable to define a clonal cell population. Some of these disorders may be the result of abnormalities in cells derived
from early stages of lymphocyte development prior to lineage commitment. In the case of commitment to T-cell differentiation, one expects that rearrangement of TcR α or complete rearrangement (VDJ) of the TcR β and TcR δ will have occurred. For commitment to the B-cell lineage, complete VDJ rearrangement of the IgH with or without rearrangement of the IgL genes is required. The rearrangement of TcR γ or partial rearrangements (DJ) of TcR β, TcR δ (VD), and IgH (DJ) are not indicative of either T- or B-cell lineages.

In our opinion, complex cross-lineage rearrangement patterns within the lymphoid neoplasms are a reflection of a malignancy that is derived from an early noncommitted lymphoid progenitor in the various lymphoproliferative disorders. This postulation is buttressed by the findings that leukemias of the more mature lymphocytes (B-CLL, T-CLL, ATL) have very low incidence of cross-lineage rearrangements. Genetic deregulation as a result of malignant transformation, referred to as lineage infidelity or promiscuity, may be responsible for a minority of the cross-lineage rearrangements in some lymphoid and nonlymphoid (eg, AML) malignancies. In addition, chromosomal translocations are also involved in a small proportion of the rearrangements in these malignancies.

Thus, the study of rearrangement patterns using multiple gene probes to TcR and Ig loci is a valuable addition to the investigation of lymphoproliferative disorders. The summary in Table 1 clearly illustrates these points. It is hoped that this summary will serve as a guide for further studies. At present, there is a need for additional studies, including clinical correlation, to decide whether a more sophisticated genotypic analysis of lymphoproliferative disorders is of prognostic significance or will someday influence the choice of therapeutic regimen for these diseases. The presence of more than two IgH genes in childhood precursor B-ALL, without an extra chromosome 14, has already been shown to be correlated with a risk of early relapse. Furthermore, studies have also recently suggested that patients with AILD, which contain clonal rearrangements of both TcR and Ig genes, may have poorer prognoses compared to those with only clonal TcR rearrangements.

Finally, it is also reasonable to expect that, as more cases of lymphoproliferative disorders with translocations involving TcR or Ig genes (especially TcR α-δ) are analyzed in detail, new proto-oncogenes will be cloned and the mechanism of activation of these proto-oncogenes will be elucidated, thus providing further insight into lymphocyte development and tumorigenesis.

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Gene rearrangements and translocations in lymphoproliferative diseases

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