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Mechanism of the t(14;18) chromosomal translocation: Structural analysis of both derivative 14 and 18 reciprocal partners

(B lymphocyte/follicular lymphoma/immunoglobulin genes/recombination/"*N*" segment/oncogene)

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ABSTRACT **To elucidate the mechanism of the t(14;18)(q32;q21) chromosomal translocation found in follicular lymphoma, we examined the structure of both derivative (der) chromosomal breakpoints as well as their germ-line predecessors. We noted that chromosome segment 18q21 was juxtaposed with immunoglobulin heavy (H) chain gene diversity (D_H) regions on all five der(18) chromosomes we examined, and we confirmed the juncture with immunoglobulin H-chain gene joining (J_H) regions on the der(14) chromosome. However, the t(14;18) was not fully reciprocal in that chromosome 14 DNA between the D_H and J_H regions was deleted. Furthermore, extra nucleotides, reminiscent of "*N*" segments, were present at the der(14) and possibly der(18) junctions. This indicates that despite the mature B-cell phenotype of follicular lymphoma, the t(14;18) occurs during attempted D_H–J_H joining, the earliest event in immunoglobulin rearrangement in a pre-B-cell. Our detailed analysis of the germ-line 18q21 region indicated that most breakpoints clustered within a 150-base-pair major breakpoint region. However, we found no evidence for evolutionarily conserved immunoglobulin-like recombinational signals at 18q21, arguing against a role for immunoglobulin recombinase in chromosome 18 breakage. Instead, a direct repeat duplication of chromosome 18 sequences was discovered at both chromosomal junctures, typical of the repair of a naturally occurring staggered double-stranded DNA break. These results prompt a translocation model with illegitimate pairing of a staggered double-stranded DNA break at 18q21 and an immunoglobulin endonuclease-mediated break at 14q32 and with *N*-segment addition, repair, and ligation to generate der(14) and der(18) chromosomes.**

Specific chromosomal translocations are highly associated with distinct neoplasms, implicating them in the origin or maintenance of malignancy (1, 2). These translocation breakpoints have been noted near previously identified oncogenes or new putative transforming genes, suggesting that they deregulate expression of these genes and play a direct role in tumor development (3). More than 80% of follicular B-cell lymphomas possess a t(14;18)(q32;q21) chromosomal translocation (4). Some of us and others (5–7) have cloned and characterized the site of chromosomal juncture on the derivative (der) chromosome 14 and identified a new transcriptional unit (BCL2) at 18q21. This interchromosomal recombination juxtaposed the immunoglobulin heavy (H) chain joining region (J_H) with the potential transforming gene on chromosome 18.

Despite the molecular cloning of the der(14) chromosomal breakpoint, the precise mechanism by which this interchromosomal recombination occurs remained unresolved. We approached this question in t(14;18) lymphomas by comparing both germ-line substrates at 14q32 and 18q21 with both derivative products of this recombination. The observation that the site of juncture on the der(14) chromosome occurred at the 5′ ends of J_H regions suggested that immunoglobulin recombinase may be mediating the breakage on chromosome 14 (5–7). In contrast, our analysis of chromosome 18 and its products indicates that its mechanism of DNA scission is a staggered double-stranded DNA (dsDNA) break unrelated to immunoglobulin recombinase. We have noted that the t(14;18) exchange does not fully conserve immunoglobulin information because the der(18) junction occurs at the H-chain diversity segment (D_H), but the der(14) junction occurs at J_H.

MATERIALS AND METHODS

Genomic Blot Hybridization. High molecular weight genomic DNA was isolated from neoplastic cells or cell lines, digested with the appropriate restriction endonuclease, electrophoresed in 0.9% agarose gels, and transferred to nitrocellulose filters as described (5, 8). Blots were hybridized with random-primed ^{32}P-labeled DNA fragments and washed at 52°C in 15 mM NaCl/1.5 mM sodium citrate, pH 7.0/0.1% $NaDodSO_4$ (5).

DNA Probes. The J_H probe was a 6.0-kilobase (kb) *Bam*HI–*Hin*dIII genomic fragment (9), and the D_H segment probe was a combination of 1.8-, 3.15-, and 4.3-kb germ-line *Bam*HI fragments representing three different D_H families (ref. 35 and U. Siebenlist, unpublished observations). The 1.5-kb *Hin*dIII–*Eco*RI fragment of chromosome segment 18q21 was isolated from the der(14) chromosomal breakpoint of the cell line SU-DHL-6 (5).

Cloning the Germ-Line 18q21 Region and der(18) Chromosomal Junction. A genomic cosmid library (a gift of David Cohen) was screened with the 1.5-kb *Hin*dIII–*Eco*RI chromosome 18 probe to obtain the germ-line region of chromosome 18. To isolate the der(18) chromosomal junction, DNA from the cell line SU-DHL-6 was digested to completion with *Bam*HI, and the fragments were ligated into the *Bam*HI arms of the phage vector Charon 28 and packaged *in vitro* (10). Recombinant phages were screened by the Benton and Davis procedure (11). Appropriate plasmid subclones were made from both types of isolates and further characterized by restriction mapping, hybridization, and DNA sequencing.

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Abbreviations: der, derivative; H chain, heavy chain; D_H and J_H, diversity and joining segments of the H-chain genes; kb, kilobase(s); bp, base pair(s); MBR, major breakpoint region; dsDNA, double-stranded DNA.

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DNA Sequencing. DNA fragments were subcloned into M13 phage vectors, and their sequences were determined by the dideoxy chain-termination method (12). Deletional subcloning from the *Eco*RI site (13) was utilized in addition to directional and shotgun cloning. Synthetic oligonucleotide primers were also utilized to sequence remaining regions of the clones.

RESULTS

The 18q21 Major Breakpoint Region Lacks Classical Immunoglobulin Recombinational Signals. To further characterize the mechanism of the t(14;18) recombination, we first isolated and analyzed the germ-line region of chromosome 18q21 involved in translocation. A human cosmid library was screened with a 1.5-kb *Hin*dIII–*Eco*RI portion of chromosome segment 18q21 obtained from the der(14) chromosomal breakpoint of the SU-DHL-6 cell line. A 45-kb germ-line region of 18q21 was obtained, and the chromosomal orientation and partial restriction map of the region predominantly involved in translocation is shown in Fig. 1 (6, 7). By Southern blot analysis of follicular lymphomas, some of us (5, 15, 16) had demonstrated that >70% of the 14;18 breaks occur within a small 2.8-kb *Eco*RI–*Hin*dIII major breakpoint region (MBR) (Fig. 1). Therefore, we determined the nucleotide sequence of this region to identify the precise sites of chromosomal breakage and to search for recombinatorial signals. Six of the seven molecularly defined breakpoints in the literature were remarkably clustered within a 150-bp region (Fig. 1) (5–7, 14). This region was extensively examined for the presence of evolutionarily conserved immunoglobulin-like recombinatorial signals utilizing the canonical heptamer (CACAGTG)–spacer (10–12 bp)–nonamer (ACAAAAACC) that represents the ideal reciprocal signal for the sequences flanking J_H (17, 18). In addition, the MBR also was searched for the precise heptamer and nonamer of the J_H region (J_6) used in the SU-DHL-6 translocation. A computer-generated randomly shuffled homology test with no mismatch limit revealed no striking homologies with immunoglobulin recombinatorial signals. The closest region within the cluster site had only 9 of 16 bp homologous with the heptamer/nonamer, and it did not flank any of the actual breakpoints. Closer homologies were identified within randomly selected sequences from GenBank,¶ including *Escherichia coli* and bacteriophage. Furthermore, no highly conserved heptamer sequences nor even TG dinucleotides (19) were found at the actual sites of chromosomal breakage within the MBR. This combination of findings prompted us to look for other explanations for the DNA breakage on chromosome 18.

A D_H Region Is Joined to Chromosome 18 on the der(18) Partner in SU-DHL-6. We wished to determine the fate of each base pair at the site of breakage on chromosomes 14 and 18 by analyzing both reciprocal partners of this exchange. The der(18) chromosomal breakpoint from SU-DHL-6 was identified on Southern blots by its differential hybridization with the 2.8-kb *Eco*RI–*Hin*dIII and 1.5-kb *Hin*dIII–*Eco*RI 18q21 probes. Since SU-DHL-6 breaks within the 2.8-kb MBR, this probe recognizes the site of interchromosomal rearrangement for both the der(14) and der(18) chromosomes (Fig. 2). In contrast, the 1.5-kb *Hin*dIII–*Eco*RI probe is telomeric to the breakpoint site, moves to the der(14) chromosome, and consequently detects only the der(14) rearrangement (Fig. 2). We utilized this fact to replica-screen a *Bam*HI genomic library of SU-DHL-6 with the 2.8-kb and 1.5-kb probes and to select the clones hybridizing exclusively with the 2.8-kb probe.

A 12.0-kb *Bam*HI fragment containing the 18;14 junction of the der(18) chromosome was isolated, and its restriction map and DNA sequence at the area of juncture are shown in Fig. 3. As the initial Southern blot suggested (Fig. 2), the chromosome 14 information flanking the der(18) juncture was not the J_1–J_5 portions of the J region as might be expected in SU-DHL-6. Instead, the site of juncture with 18q21 was within the D_H regions (Fig. 3). Two D_H regions were identifiable near the junction, and the most telomeric D_H had intact 5′ and 3′ immunoglobulin recombinational signals (heptamer–12-bp spacer–nonamer), while the most centromeric D_H region had

¶National Institutes of Health (1986) Genetic Sequence Databank: GenBank (Research Systems Div., Bolt, Beranek, and Newman, Cambridge, MA), Tape Release 40.0.

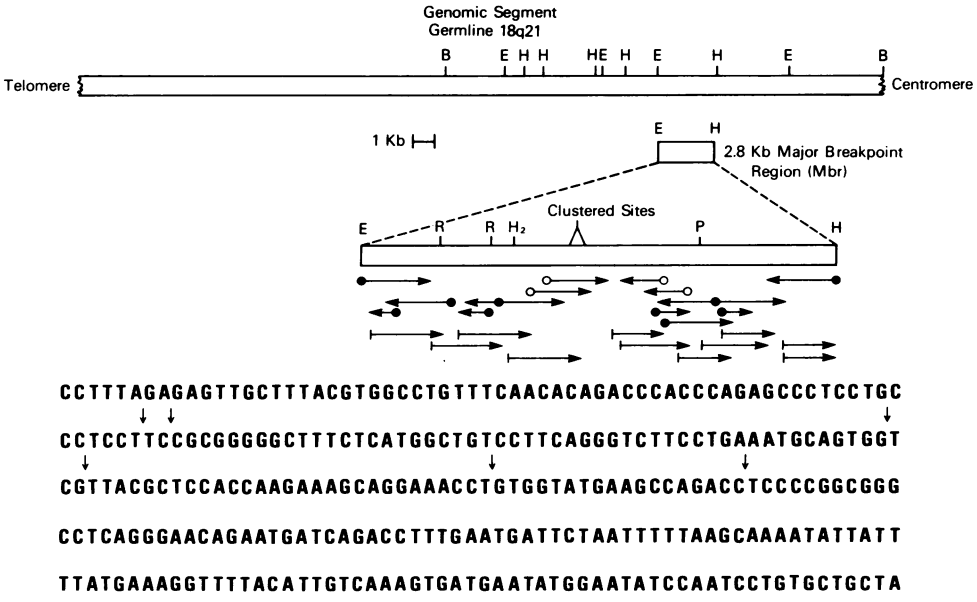

FIG. 1. The chromosomal orientation and partial restriction map of a 45-kb cosmid clone of chromosome segment 18q21. A more detailed restriction map of the 2.8-kb MBR, the sequencing strategy, and the nucleotide sequence around the clustered break sites are shown below. The six molecularly determined breakpoints (5–7, 14) are indicated by the vertical arrows. At the ends of horizontal arrows, closed circles represent directionally cloned fragments, vertical lines represent deletion subclones, and open circles represent oligonucleotide primers. E, *Eco*RI; B, *Bam*HI; H, *Hin*dIII; R, *Rsa* I; H_2, *Hpa* II; P, *Pvu* II.

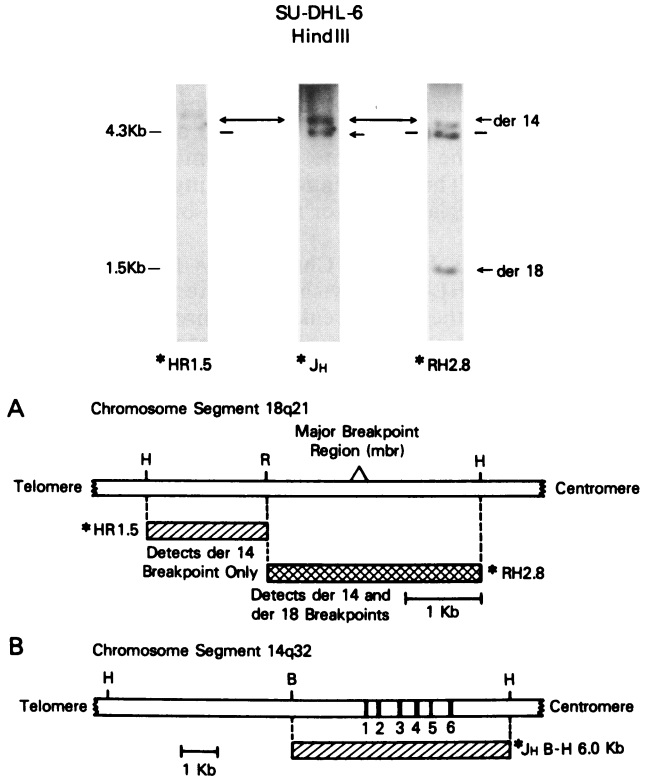

FIG. 2. Southern blot analysis of SU-DHL-6 DNA. Genomic DNA was digested with *Hin*dIII and hybridized with the J_H chromosome 14 probe and the 1.5-kb and 2.8-kb chromosome 18 probes. The der(14) chromosomal breakpoint is detected as a common rearranged *Hin*dIII fragment hybridizing with the J_H, 1.5-kb, and 2.8-kb probes (double-headed arrows). The 2.8-kb MBR probe detects an additional rearranged fragment representing the der(18) chromosomal breakpoint (arrow). (*A*) Chromosome segment 18q21 probes. (*B*) Chromosome segment 14q32 J_H probe.

deleted its 3′ signals before recombining with chromosome 18. Of note, this D_H region was 13 bp longer than its neighboring D_H region, suggesting the possibility that "*N*" segment additions, as have been described at the der(14) junctions, may occur at the der(18) junction as well.

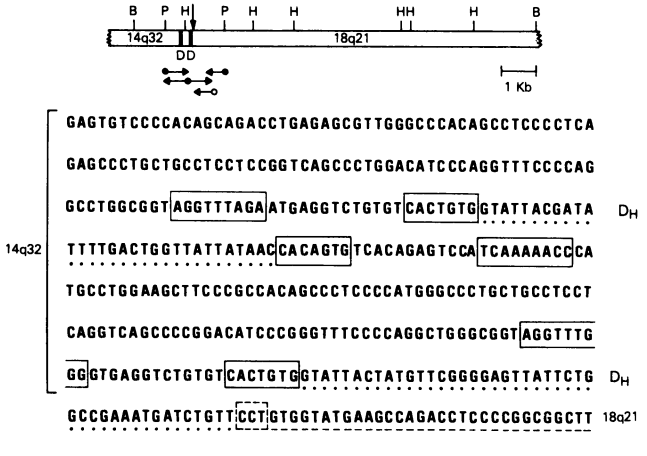

FIG. 3. (*Upper*) Restriction map with a vertical arrow showing the chromosomal breakpoint. P, *Pvu* II; B, *Bam*HI; H, *Hin*dIII. (*Lower*) DNA sequence at the 14;18 juncture on the der(18) chromosome in SU-DHL-6. The D_H regions are underlined by dots, the heptamer and nonamer recombinational signals are boxed, and the 18q21 sequences are underlined by dashes. The broken box shows the 18q21 sequences duplicated during the translocation.

18q21 Sequences Are Duplicated at the Sites of Juncture in SU-DHL-6. The nucleotide sequences at the site of chromosomal juncture on both the der(14) and der(18) chromosomes are compared with the germ-line J_H region of 14q32 and the germ-line MBR of 18q21 in Fig. 4. The heptamer–spacer–nonamer recombinatorial signals 5′ to J_6 were deleted on the der(14) chromosome and replaced with 11 extra nucleotides of unknown origin (*N* segments) (20) and flanking 18q21 information. As just presented, the der(18) chromosome introduced a D_H segment into 18q21 so that the chromosome 14 information was not totally conserved. In contrast, every base pair of germ-line 18q21 information could be found within either the der(14) or der(18) chromosome, including a trinucleotide (CCT) duplication found in both. Duplicated short stretches of DNA are typical of the direct repeats that flank DNA insertions in naturally occurring staggered double-strand breaks in genomic DNA (21).

Other t(14;18) Translocations also Break at D_H on the der(18) Chromosome. Having demonstrated loss of the 5′ J_H region in SU-DHL-6, we wished to determine if the region between D_H and J_H was routinely deleted in t(14;18) lymphomas. Genomic DNA from four t(14;18)-bearing lymphomas was digested with *Hin*dIII and hybridized with J_H and D_H chromosome 14 probes and with the 2.8- and 1.5-kb chromosome 18 probes capable of discriminating the der(14) versus der(18) rearrangements. As expected, all four t(14;18) lymphoma biopsy samples demonstrated J_H information on the *Hin*dIII fragment bearing the der(14) breakpoint that is recognized by both the 2.8-kb and 1.5-kb 18q21 probes (Fig. 5). However, none of these four nor any lymphoma we have examined possessed J_H regions on the der(18) chromosome that hybridize with only the 2.8-kb but not with the 1.5-kb 18q21 probe. In contrast, the der(18) rearrangement hybridized to a D_H region probe in all cases (Fig. 5). Therefore, the t(14;18) translocation does not interrupt a germ-line H-chain region. Instead, chromosome 18 is inserted into a H-chain locus in which the intervening information between J_H and D_H has been removed (20).

DISCUSSION

To assemble their antigen-specific receptor molecules, B and T lymphocytes must somatically recombine separate germline DNA segments (22, 23). This joining involves the recognition of conserved heptamer–spacer–nonamer signals bordering each gene segment, dsDNA cuts, frequent *N* segment addition, and religation to unite the ends of the same chromosome. Within lymphoid neoplasms these same loci are remarkably the sites involved in recombination with other chromosomes. In this and other studies, all molecularly determined der(14) chromosomal breaks of the t(14;18) translocation occur site specifically at the 5′ end of immunoglobulin J_H regions, and extra nucleotides are found at the juncture of the J_H region and 18q21 (5–7, 14). Moreover, in this study we have demonstrated that the 14;18 translocation is not fully reciprocal but that chromosome 14 information normally residing between D_H and J_H is deleted in all five cases examined. The juxtaposition of chromosome 18 with D_H segments on one chromosome and with J_H on the other indicates that immunoglobulin recombinase is responsible for an endonucleolytic cleavage of dsDNA on chromosome 14. The presence of *N* segments at the chromosomal junctures is an additional argument that this translocation occurs at a pre-B-cell stage of development, when recombinase and presumably terminal deoxynucleotidyl transferase are active (24). Moreover, this supports a previously proposed distinct step in normal immunoglobulin gene joining in which there are endonucleolytic breaks at the 3′ end of D_H and 5′ end of a J_H segment, with loss of intervening information prior to their juxtaposition and religation (20).

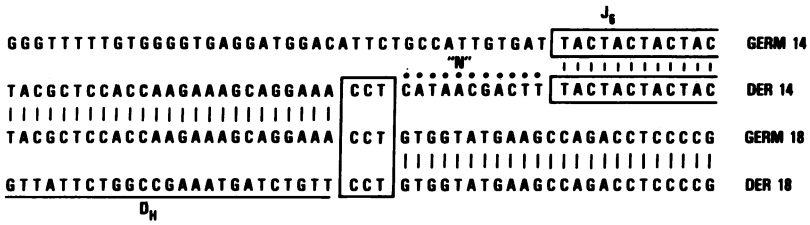

FIG. 4. Nucleotide sequence comparison of the germ-line chromosomes 14 and 18 and the der(14) and der(18) reciprocal partners. DNA sequences are oriented telomere (5′) to centromere (3′) from left to right. Vertical lines indicate nucleotide homology between adjacent sequences. The 11 *N*-region nucleotides at the der(14) junction are marked by dots, and the D_H sequences introduced at the der(18) junction are underlined. The trinucleotide CCT present in the germ-line 18q21 region and at both der(14) and der(18) junctions is boxed.

In contrast to the hypothesis proposed by Tsujimoto *et al.* (6), the data presented here argue that chromosome 18 scission does not involve recognition of immunoglobulin-like recombination signals and cleavage by immunoglobulin recombinase. First, the major breakpoint region (MBR) lacked highly conserved immunoglobulin-like recognition sequences resembling a palindromic heptamer (CACAGTG), a 12-bp spacer, and an A+C-rich nonamer that would pair with J_H. Moreover, the "12/23" spacer rule requires that immunoglobulin recombinase juxtapose segments having 12-bp spacers with segments having 23-bp spacers (17, 18). Thus, the presence of D_H/18 junctions on the der(18) chromosome would require the 18q21 MBR to also possess a reciprocal set of recognition signals that are in the opposite orientation and have 23-bp spacers. It seems unlikely that such a dual set of recombinational signals would be maintained at 18q21, and a computer search confirmed this. Second, while isolated heptamers have been noted at some sites of recombination in the immunoglobulin loci (25, 26), no highly conserved heptamers abut the breakpoints. Third, this region of 18q21 does not intrinsically rearrange during normal B-cell development, indicating that no evolutionarily conserved functional recombination occurs here (5). Thus, a mechanism other than immunoglobulin recombinase-mediated cleavage appears responsible for the breaks at 18q21.

The sequence analysis of all four chromosomal participants, including the germ-line substrates at 14q32 and 18q21 and both der(14) and der(18) products, provided clues into the translocation process. Notably, a duplication of chromosome 18 sequences occurred at the juncture site of both the der(14) and der(18) chromosomes. The duplication of DNA sequences flanking the insertion of foreign DNA is typical of the direct repeats that result from the repair of naturally occurring staggered double-strand breaks (21). In this setting, where the inserted DNA represents a reciprocal chromosomal translocation, the flanking direct repeats would be located at the juncture site on both derivative partners. Consequently, we propose a model of t(14;18) translocation in which a pre-B-cell undergoes an illegitimate pairing of D_H and J_H ends on chromosome 14 with a staggered double-

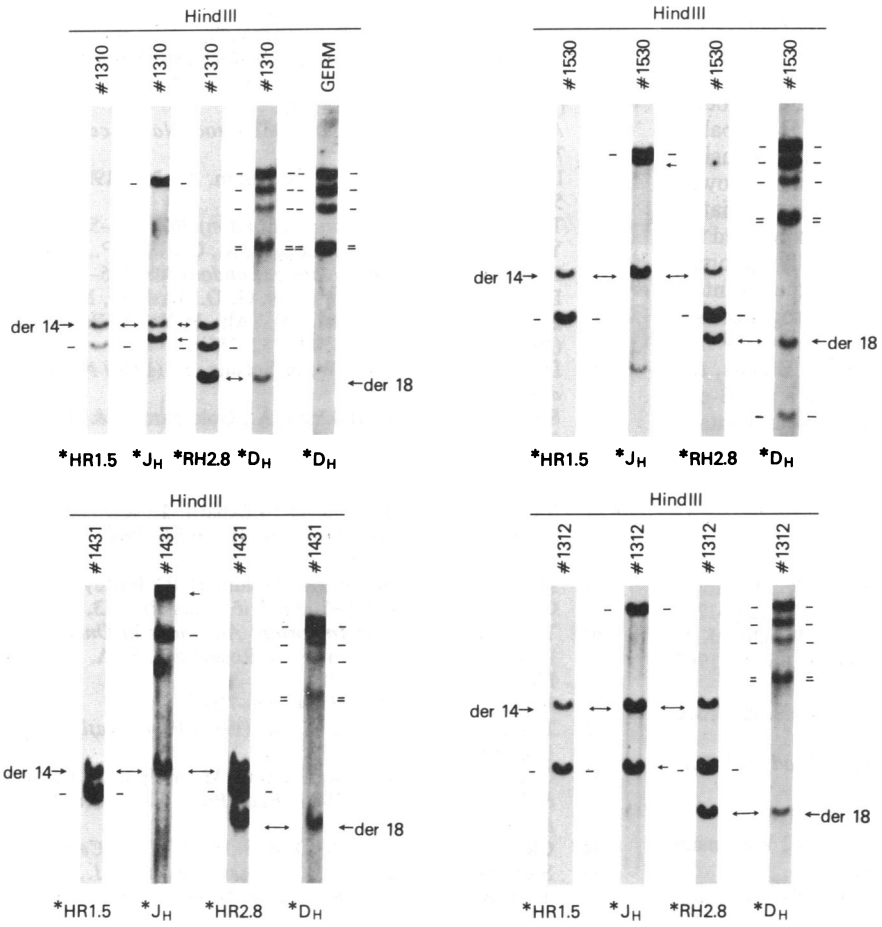

FIG. 5. Comigration of restriction fragments containing sequences from chromosomes 14 and 18 in t(14;18) lymphoma biopsy tissues identified by number at the top of each lane. Southern transfers of *Hin*dIII-digested genomic DNAs were hybridized to the probes indicated at the bottom of each lane with an asterisk. The germ-line fragments recognized by each probe are indicated by dashes, and the rearranged fragments by arrows. Comigrating fragments are indicated by dual-headed arrows. All four cases demonstrate J_H information on the der(14) chromosome recognized by the HR1.5 and RH2.8 probes. In contrast, the der(18) chromosome (recognized by the RH2.8 but not the HR1.5 probe) hybridized to the D_H probes but not to the J_H probe.

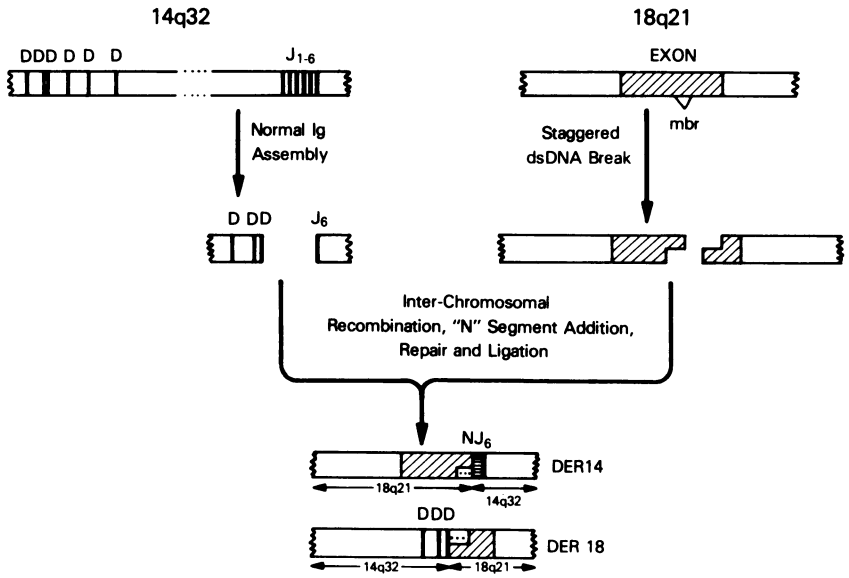

FIG. 6. Mechanism of the t(14;18) translocation. An illegitimate pairing of the four fragments generated by an immunoglobulin endonuclease-mediated break at 14q32 (*Left*) and a staggered dsDNA break at 18q21 (*Right*) results in the der(14) and der(18) chromosomes. The diagonally hatched box represents the 3′ exon of the BCL2 gene; the horizontally hatched box, *N* segment addition; and the dotted box, a direct-repeat duplication.

strand break on chromosome 18 (Fig. 6). *N* nucleotides are added at the ends of chromosome 14, the single-stranded regions of 18 are "filled in" by polymerase, and the 14/18 ends are ligated to generate the der(14) and der(18) products. Similar analyses of all four chromosomal participants have been conducted in mouse plasmacytomas (27, 28) and Burkitt lymphoma (29). Gerondakis *et al.* (27) discovered a c-*myc* region duplication in a murine plasmacytoma and proposed a similar staggered nick model for the t(15;12) translocation.

Staggered dsDNA breaks may occur randomly in genomic DNA. This implies that a functional reason exists for the clustering of breakpoints within the MBR on 18q21. The 18q21 segment has been designated a constitutive fragile site (FRA18B) by Yunis and may relate to the clustered breakpoints (30). We could find no obvious core sequences that might enhance homologous recombination within the MBR, including *chi* sequences (GCTGGTGG) that have been noted in immunoglobulin and MYC loci (31). It is probable that breakage of chromosome segment 18q21 and its fusion with J_H may be an extremely rare event that confers a growth advantage. We and others have identified a B cell-associated gene (designated BCL2) on 18q21 that is overly expressed for a mature B-cell stage of development in t(14;18) lymphomas (5–7). The chromosomal fusion with chromosome 14 interrupts a 3′ exon of this gene, resulting in heterogeneously sized transcripts and perhaps deregulation (32–34). While follicular lymphomas are phenotypically mature B cells, the t(14;18) appears to occur early in development at a pre-B-cell stage. This translocation may offer a proliferative advantage but requires additional complementing genetic changes at later steps to achieve full transformation.

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