Rearrangement of Rat Immunoglobulin E Heavy-Chain and *c-myc* Genes in the B-Cell Immunocytoma IR162

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Mammalian B-cell lymphoid malignancies frequently display aberrant translocations involving the *c-myc* proto-oncogene and one of the immunoglobulin loci. We have observed and characterized such a translocation in the immunoglobulin E-producing rat immunocytoma IR162 by using recombinant DNA technology. We show here for the first time that a *c-myc* gene has recombined with the excluded allele of the nonfunctional epsilon heavy-chain immunoglobulin gene. This recombination has resulted in the loss of 5'-proximal DNA and, consequently, potential regulatory information from the body of the *c-myc* structural gene via joining to the epsilon heavy-chain switch region in a head-to-head, i.e., 5'-to-5', configuration. As discussed in this report, these results, together with the previous results of others, have important implications for immunoglobulin heavy-chain class switching mechanisms controlling normal and abnormal translocations.

Specific chromosomal translocations observed in several human and animal tumors are believed to be very important in tumorigenesis. A well-characterized example occurs in both mouse plasmacytomas and human Burkitt lymphomas, in which a chromosomal translocation juxtaposes the *c-myc* proto-oncogene to an immunoglobulin locus, usually that of the heavy (H) chain (3, 4, 12, 13, 15, 17, 20). This translocation is thought to result in deregulation of *c-myc* proto-oncogene expression in these B-cell tumors (2, 23). It is also known that a *T(6;7)* chromosomal translocation involving the *c-myc* gene occurs in many LOU/Ws1 rat spontaneous immunocytomas (28), most of which usually secrete monoclonal immunoglobulin E (IgE) (H. Bazin, Adv. Cancer Res., in press). Therefore, the purpose of this study was to determine whether an immunoglobulin locus might also be involved in these rat *c-myc* translocations, thus further demonstrating the significance of *c-myc* gene rearrangements in B-cell tumorigenesis.

Rearrangement and juxtaposition of the *c-myc* gene and excluded allele of the epsilon H-chain gene of the IgE-producing immunocytoma IR162. A genomic DNA library of the rat IgE-producing immunocytoma IR162 was constructed in the lambda bacteriophage EMBL-4 (8). The tumor DNA was partially digested with restriction enzyme *CpfI* and size fractionated on a 10 to 40% sucrose gradient. Fractions in the size range of 10 to 20 kilobase pairs (kbp) were pooled, ligated into the compatible *Bam*HI sites of EMBL-4, packaged in vitro, and plated on the *Escherichia coli* host LE392 (14). This library was then screened by plaque hybridization for epsilon H-chain immunoglobulin (hereafter referred to as epsilon) and *c-myc* genes with the pe.C and the *c-myc*.4 probes (all probes used for the entire study are shown in Fig. 1). Restriction enzyme map analyses of all clone types isolated and characterized (two types for *c-myc* and three types for epsilon) are shown in Fig. 2A to D. All DNA clones were mapped by single and double restriction enzyme digestions with the restriction enzymes shown. Clones M1 and 1CE appeared to contain the entire rat *c-myc* gene, as inferred from the mouse analog, but differed at their 5' ends (Fig. 2A and B). Likewise, all the epsilon-specific

clones displayed homology at their 3' ends but differed at their 5' ends (Fig. 2B to D).

These results suggested that some of the DNAs containing the *c-myc* and epsilon genes may have undergone rearrangement. This possibility was confirmed with Southern blot analyses of DNAs from LOU rat liver and IR162 (Fig. 3). A unique *c-myc* DNA fragment was found in the IR162 DNA with *Bgl*II, *Sac*I, or *Xba*I digestion, indicating that one of the *c-myc* alleles was rearranged (Fig. 3A). These enzyme digestions also revealed two different, rearranged epsilon alleles in the IR162 DNA (Fig. 3B). (The germ line equivalent probably resulted from the nonlymphoid cells contaminating the solid tumor, as suggested from densitometry analyses of the Southern blots and knowledge that an IR162 cell culture line has a near-diploid, average chromosome content of 41 [C. H. Faust, unpublished observations].) In addition, for a given enzyme digestion, both the *c-myc* and epsilon probes hybridized to IR162 DNA fragments of identical lengths, e.g., 2.6, 5.3, and 5.7 kbp for *Bgl*II, *Sac*I, and *Xba*I, respectively. This result demonstrates that the epsilon and *c-myc* genes are contiguous on the same piece of DNA and that they might be involved in a reciprocal translocation.

The complete normal rat *c-myc* gene was identified in clone M1 with a cloned mouse cDNA probe (25). Like those of mice and humans, this putative *c-myc* gene spans about 6 kbp and contains genetic information corresponding to the three exons and two introns of the mouse probes (Fig. 1A and 2A). Because of the well-established high level of evolutionary conservation of the *c-myc* proto-oncogene among other, more distantly related species than mice and rats, we suggest that the rat *c-myc* proto-oncogene will likely also contain three exons and two introns. However, confirmation of this possibility will require more detailed structural analyses of the rat *c-myc* gene. Two other overlapping M1-type *c-myc* clones were found (data not shown), and a comparison with clone 1CE revealed homologous restriction enzyme sites from the 3' *Eco*RI site only up to the *Sma*I site near the 5' end of exon 1 (cf. Fig. 2A and B).

The organization of the three types of cloned epsilon genes was determined from the restriction enzyme maps of clones E1, E4, and 1CE and from DNA fragments which hybridized to the pe.C and pe.VC probes (Fig. 1A to D and 2B to D). Homologous restriction enzyme sites were found from the

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FIG. 1. Parental clones used as probes for these analyses and their restriction enzyme maps. The coding regions are stippled, and the exons of the parental clones are labeled or numbered in each illustration. The various cloned sources of the probes included the following: (A) the normal, full-length mouse *c-myc* cDNA, pM *c-myc*54 (7); (B) the entire normal mouse genomic *c-myc* DNA in Charon 28 (1) and a 5.5-kbp *Bam*HI mouse genomic *c-myc* DNA fragment, *c-myc*.4 (29); (C) a rat Ce region cDNA fragment, *pe.C* (5, 11; C. H. Faust, unpublished data), and a full-length, IR162-specific, VH-Ce region cDNA fragment, *pe.VC* (C. H. Faust, unpublished data); and (D) a mouse epsilon genomic DNA, Ige-12 (24), and a mouse epsilon switch region subclone, pSe, derived from it (unpublished pBR325 clone from B. Birshstein containing the 5.1-kbp *Bam*HI mouse Se region fragment [18]). Specific DNA probes, indicated by lines below the parental clones, were prepared from these by digestion with the appropriate restriction enzymes, electrophoretically separated on an agarose gel, and labeled by the random primer extension method with [32 P]dATP (6). Restriction enzymes used throughout these analyses included the following: A, *Apa*I; B, *Bam*HI; Bg, *Bgl*II; D, *Dra*I; E, *Eco*RI; G, *Bgl*II; H, *Hind*III; P, *Pst*I; Sc, *Sac*I; S, *Sma*I; and X, *Xba*I. bp, Base pairs.

3'-most *Bam*HI site up to the *Hind*III site 5' to the epsilon H-chain constant region (Ce region), encompassing the entire Ce region and its 3'-flanking region (26; C. H. Faust, unpublished data). Examination of these clones with an IR162-specific, VH (variable)-Ce region cDNA probe, *pe.VC*, detected the rearranged VH region in clone E1 only. The full-length cDNA clone *pe.VC* was characterized as belonging to the rat VH II subgroup, on the basis of the mouse classification system (10), and will be described elsewhere. The 2.1-kbp *Hind*III fragment, located between the VH and Ce regions in clone E1, was a candidate for the epsilon H-chain switch region (Se region), since it did not hybridize with any cDNA probe. This was proved by hybridization with a mouse Se region probe (18), pM-Se (Fig. 1D); two overlapping E1-type clones also validated this conclusion (data not shown).

The other two epsilon-specific clones, E4 and 1CE, did not

hybridize with the VH region probe but still differed from each other at their 5' ends (Fig. 2B to D). Clone E4 hybridized with none of the *c-myc* probes (Fig. 1A and B) and, from analogy with the mouse epsilon genomic DNA clone, represents the germ line Ce region (data not shown). However, clone 1CE hybridized with the *c-myc* probes as well as with the Ce region probe (Fig. 1A to C and 2B), demonstrating a *c-myc*-epsilon rearrangement and juxtaposition. An independent clone completely identical to clone 1CE was also found. Consequently, the IR162 DNA contained three different types of epsilon genes: (i) E1, the normal, functionally rearranged VDJ (complete variable)-Ce gene; (ii) E4, the normal, unrearranged germ line Ce gene (probably derived from cells contaminating the solid IR162 tumor); and (iii) 1CE, the Ce gene aberrantly rearranged with the *c-myc* gene. These data (Fig. 2), in conjunction with the Southern blot data (Fig. 3), demonstrated that all types of

A. Normal c-myc, M1

B. Translocated c-myc, 1CE

C. Rearranged epsilon, E1

D. Germline epsilon, E4

c-myc and epsilon genes were cloned and that no cloning artifacts were responsible for the aberrant juxtaposition of these two genes.

A 2.6-kbp *Bgl*II genomic DNA fragment hybridized on Southern blots with both the *c-myc* and epsilon DNA probes (Fig. 3). The same *Bgl*II fragment was detected in clone 1CE (Fig. 2B), indicating that it contained portions of the sequences for both *c-myc* and epsilon. Using a mouse *c-myc* exon 1 cDNA probe, pM-54.1, we localized one *Bgl*II site in clone 1CE 3' to exon 1 of *c-myc*. On the basis of hybridization with the pe.C probe, the other *Bgl*II site was localized to the 5' end of the Ce2 domain of epsilon (26; C. H. Faust, unpublished observations). The junction containing the breakpoint was localized to a 0.65-kbp region between an *Apa*I site (associated with the Se region) and an *Sma*I site (close to the 5' end of exon 1 of *c-myc*) of this subcloned 2.6-kbp *Bgl*II fragment (Fig. 2B). It is not known if this breakpoint is 5' of exon 1 or if part of exon 1 has been lost during translocation. Eventually, DNA sequencing of this *Apa*I-*Sma*I fragment and the corresponding regions of the normal genes will identify the precise breakpoint and reveal the specific sequences involved in the translocation.

Deletion of the 5'-proximal DNA region from the *c-myc* gene aberrantly translocated to the epsilon switch site of the excluded allele. Previous evidence suggested that in most mouse plasmacytoma tumors, loss or disruption of a *cis*-acting element immediately 5' of the *c-myc* gene may be responsible in part for its deregulated expression (2, 23). This region of DNA, with the potential to act as a negative regulatory element, was located a few hundred base pairs 5' of the first *c-myc* promoter (23) and independently confirmed by others (2). Since it acted in a mode similar to that of an enhancer but with an opposite effect, i.e., as a silencer, it was called a "dehancer" (23). Therefore, we examined our cloned rat *c-myc* DNAs to determine if we could detect any DNA sequence homology to the mouse dehancer in the normal *c-myc* clone M1 and in the aberrantly rearranged *c-myc*-epsilon clone 1CE. A mouse 1.4-kbp *Sac*I-*Sma*I fragment (*c-myc*.2, Fig. 1) containing only the dehancer sequence and no structural gene information (23) was isolated, labeled, and hybridized with itself, M1, and 1CE (Fig. 4). In clone M1, a 1.7-kbp *Xba*I-*Hind*III fragment containing the 5'-flanking region and part of exon 1 of *c-myc* was detected (Fig. 2A and 4), but no portion of clone 1CE (cf. Fig. 2A and B) hybridized with this mouse dehancer probe (Fig. 2B and 4). This result indicated that a rat DNA fragment located 5' to the *c-myc* structural gene and with

homology to the mouse dehancer sequence could be detected in clone M1. However, this 5'-proximal DNA region (rat dehancer candidate) was not transferred with the aberrantly rearranged *c-myc* gene to the Se region in clone 1CE.

Implications of the aberrant *c-myc*-epsilon translocation for mechanisms controlling normal and abnormal class switch recombinations. It has been shown in another study (7) that some *c-myc* gene rearrangements appear to share a common mechanism of translocation in some T- and B-cell neoplasias, involving an aberration in the VDJ type of joining machinery. Normally, this DNA recombination machinery is used to assemble a functional antigen receptor for all lymphoid cells, but on occasion it can apparently malfunction, with disastrous consequences. A second, different type of recombination which mediates normal immunoglobulin H-chain class switching occurs only in B cells. Numerous examples of B-cell tumors in mice and humans have also been found, possibly reflecting recombinational aberrations in the immunoglobulin H-chain class switching machinery because of the translocational involvement of the *c-myc* gene with the switch sites of the immunoglobulin H-chain locus (3, 4, 12, 13, 15, 17, 20). Upon translocation of the *c-myc* structural gene to an immunoglobulin H-chain DNA switch element, these B-cell tumor types frequently display the loss of a 5'-proximal DNA element of the *c-myc* gene, the so-called dehancer or silencer, which may have a negative regulatory role in its expression (2, 23).

Our work demonstrates for the first time in rats a simple type of *c-myc* translocation with the immunoglobulin H-chain locus. This translocation, which may contribute to B-cell tumorigenesis through the loss of a 5'-proximal DNA element from the *c-myc* gene, involves the synonymous, nonexpressed Ce region of the IgE-producing immunocytoma IR162. Moreover, this is the first time that an Se region has been found associated with a *c-myc* gene translocation. This is especially interesting, considering that nearly half of all LOU rat immunocytomas produce IgE (Bazin, in press), even though IgE-specific B cells are the least abundant in an organism, occurring with a frequency of as little as 1 in 10,000 B cells (27), and considering that the epsilon switch region presents the shortest switch site target (18) for translocation with the *c-myc* gene. Moreover, the translocational involvement of both synonymous immunoglobulin switch sites of IR162 is also very intriguing because, analogously, it was found that with mouse plasmacytomas, which principally produce IgA, the synonymous alpha H-chain switch region (Sa region) of the excluded allele is the

FIG. 2. Restriction enzyme map analyses of rat *c-myc* and epsilon genomic DNAs cloned from IR162. (A) Clone M1, whose total DNA insert length is 17 kbp, contains the entire normal rat *c-myc* gene. The putative exons 1, 2, and 3 are indicated, based on a comparison with the mouse DNA probes used. (B) Clone 1CE, whose total DNA insert length is 16 kbp, contains the translocated, contiguous rat *c-myc* and epsilon genes. The solid bar above the map illustrates the 2.6-kbp *Bgl*II DNA fragment, which hybridized to both *c-myc*- and epsilon-specific probes and which was subcloned into plasmid vectors pIBI 24 and pIBI 25 (derivatives of the pUC series from International Biotechnologies, Inc., New Haven, Conn. [16]). A more detailed map of this subcloned fragment is shown below the map of the full-length insert. The 0.65-kbp junctional region containing the DNA breakpoint lies below the solid triangle and between the *Apa*I and *Sma*I sites. The head-to-head transcriptional orientations of the *c-myc* and epsilon genes are shown, together with the approximate location of the rat Se region. The E1.Se probe is the 2.1-kbp *Hind*III fragment from clone E1 containing the putative rat Se region. (C) Clone E1, whose total DNA insert length is 18 kbp, typifies the normal, functionally rearranged epsilon gene VDJ-Ce. The approximate locations of the VH region, the Ce region exons, and the switch region (S region) of IR162 are indicated; presumably, the latter would be a hybrid switch [S(u)e] region formed by recombination between the germ line Su and Se sites. (D) Clone E4, whose DNA insert length is approximately 17 kbp, typifies the unrearranged germ line Ce gene. Only the Ce region and the Se region were detected. The region in parentheses 5' to the Ce exons has undergone about a 1-kbp deletion during cloning and includes only part of the Se site (data not shown). The terminal *Eco*RI sites of all cloned genomic DNAs are derived from the vector flanking the *Bam*HI insert sites of EMBL-4 (8). The entire fragment length of a cloned DNA which hybridized with a given DNA probe for a specific single or double restriction enzyme digestion is indicated by corresponding lines below the respective restriction enzyme maps. The 5'- to 3'-transcriptional directions of genes characterized in all clones are indicated with arrows. See the legend to Fig. 1 for restriction enzyme abbreviations.

FIG. 3. Southern blot analyses of LOU rat liver and IR162 genomic DNAs with *c-myc*- and epsilon-specific probes. Genomic DNAs (12 μ g) from LOU rat liver (L) and the IgE-producing immunocytoma IR162 (I) were digested to completion with the restriction enzymes *Bgl*II, *Sac*I, and *Xba*I electrophoretically separated in 0.7% agarose gels, transferred to Zetabind filters in NaOH (22), prehybridized overnight in $5\times$ SET (14)–200 μ g of carrier DNA per ml, and hybridized identically with 2.5% dextran sulfate–radiolabeled probes (14). Filter washings were done twice for 30 min each time at room temperature in $2\times$ SET and twice for 30 min each time at 65°C in $0.1\times$ SET. (A) Results of hybridization with a mouse *c-myc* probe (c-myc.3, containing exon 1 and 5'-flanking sequences [Fig. 1B]). (B) Results of hybridization with a *Hind*III-*Xba*I DNA probe (2.1 kbp) derived from clone E1 (containing all four Ce region exons of the genomic DNA [Fig. 1C] (26; unpublished data). Arrows indicate the comigrating, autoradiographic bands that were detected with both the *c-myc* and epsilon probes and that represent rearranged DNA unique to IR162 DNA and not found in LOU rat liver DNA. DNA size markers are indicated in kilobases (KB).

FIG. 4. Putative rat dehanter sequence in the normal rat *c-myc* DNA clone M1 and its absence in the translocated *c-myc*-epsilon DNA clone 1CE. Cloned M1 DNA (Fig. 1A) was digested with *Xba*I and *Hind*III, and cloned 1CE DNA (Fig. 1B) was digested with *Hind*III, and both were electrophoresed in 0.8% agarose gels and transferred to nitrocellulose. Southern blots were performed as described in the legend to Fig. 3, but without dextran sulfate. The probe used was the c-myc.2 probe (1.4-kbp *Sac*I-*Sma*I [Sc+S] fragment [4]) described in Fig. 1B, and the result of its hybridization to itself is shown in the first lane. The second lane shows the hybridization result with the rat dehanter candidate region (1.5-kbp *Hind*III [H] fragment) of clone 1CE (Fig. 1B) contained within the 2.6-kbp *Bgl*II piece. The third lane shows the hybridization result with the rat dehanter candidate region (1.7-kbp *Hind*III-*Xba*I [H+X] fragment) of clone M1 containing the normal rat *c-myc* gene (Fig. 1A). Although only the region of interest in the gel is shown, no other DNA bands present in any clone analyzed in the run hybridized to this probe (data not shown). KB, Kilobases.

most frequent *c-myc* acceptor (4). Similarly, the synonymous mu H-chain switch region (Su region) of the excluded allele was shown to be the most frequent *c-myc* acceptor in Burkitt lymphomas which produce mostly IgM (4). Switch-mediated translocations involving the excluded allele in normal mouse splenic B cells have also been found, although no correlation of the synonymous switch relative to the functionally expressed allele has been made (9, 21).

The data for these three animal species suggest that some *c-myc* gene translocations are closely associated with immunoglobulin class switching and strongly implicate an aberration in the B-cell switching machinery in this process, while also suggesting an immunoglobulin class switch site preference for *c-myc* gene translocation. This abnormal translocation appears to favor selection of the switch site of the excluded H-chain allele synonymous with that of the expressed immunoglobulin class of the functionally normal H-chain allele. Moreover, although normal switching is generally believed to occur with only one of the two immunoglobulin alleles, data from mouse, rat (described here), and human studies for both normal and malignant B cells suggest that briefly during the ontogeny of B cells, both homologous immunoglobulin alleles may synchronously exist in a genetically metastable, activated state, such that the excluded allele is potentiated for aberrant translocation by the switching machinery, and that occasionally this may involve the *c-myc* proto-oncogene. If this speculation were correct, we might expect this simple type of *c-myc*-epsilon translocation to be found with high frequency as the initial switch-mediated translocation event among the other known IgE-producing immunocytomas of LOU rats. Information on the timing of the switch of monoclonal IgM-producing B

cells to the eventual IgE-producing B cells and the genetic state of the Se region of both alleles would provide additional clues for a better understanding of the mechanisms of both normal immunoglobulin class switching and *c-myc* translocation.

During the preparation of this manuscript, an unusually complex *c-myc* translocation in another rat immunocytoma was reported (19). These authors suggested that multiple chromosomal rearrangements juxtaposed *c-myc*, the Su region, and the C γ 1 region (domain 1 of the γ H-chain constant region). Our study confirms that, as in most Burkitt lymphomas and mouse plasmacytomas, *c-myc* translocations to immunoglobulin loci are probably common in rat immunocytomas.

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