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Organization of four mouse \( \lambda \) light chain immunoglobulin genes

gene cloning/variable, joining, and constant segments/electron microscopy

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**ABSTRACT** We have cloned four \( \lambda \) light chain constant region (C) genes from mouse embryo DNA. Each carries its own joining (J) segment approximately 1.3 kilobases to its 5′ side. The four C genes occur in two clusters, 5′ \( J_2C_2J_1C_1 \) and 5′ \( J_2C_2J_1C_1 \), with \( C_4 \) being a new CA gene. We have also shown that \( V_{ \lambda 1} \) is joined productively with \( C_{ \lambda 4} \) in an \( \lambda _{ \text{CA}} \)-producing myeloma, and it is most likely that \( V_{ \lambda 1} \) and \( V_{ \lambda 2} \) are the only \( V \lambda \) genes. Based on the analysis of the germ line and rearranged variable region (V) \( \lambda \) genes in myelomas we argue that the \( V_{ \lambda 1} \) and \( V_{ \lambda 2} \) genes are at the 5′ side of the \( C_2C_2 \) and \( C_4C_4 \) clusters, respectively. We propose that the two clusters arose by duplication. We also speculate on the role of J-associated DNA sequences in regulation of expression of the \( \lambda \) subtypes.

The immunoglobulin genes occur in three families: one for the heavy chain, and one each for the two light chains, \( \kappa \) and \( \lambda \). It has been well established that the variable (V) and constant (C) region genes are somatically rearranged during differentiation of lymphocytes (1, 2). In the case of light chains, the V DNA segment, encoding amino acid positions 1–97, joins directly with a joining (J) DNA segment that encodes positions 98–107, thereby creating a complete V gene (3). The J DNA segment is within a few kilobases to the 5′ side (upstream) of the C gene. Production of a complete heavy chain V gene requires joinings of three types of germ-line DNA segments—V, D, and J (4, 5) (the D DNA segments encode primarily the third hypervariable region). Somatic joinings of the two (V, J) or three (V, D, and J) types of germ-line gene segments in various combinations contribute greatly to the amplification of antibody diversity.

The \( \lambda \) light chains, which are present in only about 5% of total serum immunoglobulin in the mouse (6, 7), are of three subtypes, \( \lambda_1 \) (or \( \lambda_{11} \)) (8, 9), \( \lambda_2 \) (or \( \lambda_{12} \)) (10), and the newly described \( \lambda_3 \) (or \( \lambda_{13} \)) (11). In most mouse strains, \( \lambda_1 \) accounts for about 80–90% of all \( \lambda \) chains (7). Each of the \( \lambda \) subtypes must be encoded by its own constant region (CA) gene. Although the molecular structure and organization of the \( \lambda_1 \) and \( \lambda_2 \) C genes were the first to be extensively studied (2, 3, 12), the physical relationship among the various \( \lambda \) subtype genes is unknown.

We were interested in determining a molecular basis for the dominant expression of the \( \lambda_1 \) subtype and for the preferential joining of \( \lambda_1 \) with \( C_{ \lambda 1} \) and of \( \lambda_2 \) with \( C_{ \lambda 2} \), as seen in \( \lambda \) myeloma proteins. Additionally, we wanted to know if each \( \lambda_1 \) gene carried its own J segment to its 5′ side, or if there were a cluster of J segments as in the \( \kappa \) (13, 14) and heavy chain systems (4, 5).

In this report we describe four \( \lambda \) genes and give their molecular organization. We also show that the \( V_{ \lambda 1} \) DNA segment is joined with the \( J_{ \lambda 1}C_{ \lambda 1} \) DNA segment in the complete \( \lambda_1 \) gene active in a \( \lambda_1 \) myeloma. We argue that the probable order of the various \( \lambda \) gene segments is \( J_{ \lambda 1}C_{ \lambda 1}J_{ \lambda 1}C_{ \lambda 1} \), and \( V_{ \lambda 1}J_{ \lambda 1}C_{ \lambda 1}J_{ \lambda 1}C_{ \lambda 1} \), in which \( J_{ \lambda 1} \) designates a new CA gene.

**MATERIALS AND METHODS**

**Bacteria and Phages.** Phage Charon 4A was obtained from F. Blattner (University of Wisconsin, Madison, WI) (15). The AgtWES-AB was from P. Leder (National Institutes of Health) (16). Escherichia coli 803 (K+ m3, F+ ) was originally from K. and N. E. Murray (University of Edinburgh). Lysozymes used for preparation of packaging mixtures, BHB 2688 [N205 recA- (Aimm43, b2red3 Eam4 Sam7/A) and BHB 2690 [N205 recA- (Aimm43, c1, b2red3 Dam 15 Sam7/A] were obtained from B. Hohn (Friedrich Miescher Institute) (17).

**Preparation of Mouse Embryo Libraries and Cloned DNA Fragments.** EcoRI partial libraries in bacteriophage A were prepared as described (18). Preparation of high molecular weight DNA, preparative agarose gel electrophoresis, and extraction of DNA from agarose have been reported (1). Ligation, transfection, and plaque screening of cloned DNA with nick-translated probes were performed as described (19). All cloning experiments were performed under P3-EK2 conditions in accordance with the National Institutes of Health guidelines for recombinant DNA research, issued in 1976.

**Gel Blotting of DNA Fragments.** Cellular and cloned DNA fragments produced by restriction enzyme cleavage were transferred from agarose gels to nitrocellulose filters according to the procedure developed by Southern (20).

**Electron Microscopy.** Procedures for preparing single-stranded and double-stranded DNA/mRNA hybrids, DNA heteroduplexes, and B hybrids have been described (21).

**Other Procedures.** Purification of \( \lambda \) chain mRNAs of \( \lambda_1 \) (H2020), \( \lambda_2 \) (MOPC315), and \( \lambda_3 \) (BCP49) has been described (1). The hybridization probes were nick-translated cDNA prepared from MOPC315-containing (V + C)\( \lambda_2 \) (a gift from R. Schwartz and M. Getfer), 600 base pairs complementary to \( C_{ \lambda 1} \) from an Hha I/Hae III digest of the B1 plasmid of H2020 cDNA (V + C)\( \lambda_1 \) (19), or 330 base pairs from the Hha I/Hae III digest of B1-H2020 \( \lambda_1 \) containing only the V and J regions [V(J)\( \lambda_1 \) probe].

**RESULTS**

Identification of Four EcoRI Fragments Carrying CA Sequences. High molecular weight total cellular DNA was extracted from kidneys of three mouse strains and digested with EcoRI endonuclease, and the resulting DNA fragments were analyzed by the Southern gel blotting technique. The hybridization probe was either (V + C)\( \lambda_2 \) cDNA (Fig. 1A) or CA\( \lambda_1 \) cDNA (Fig. 1B). With (V + C)\( \lambda_2 \), we usually saw four bands, at 8.6, 4.8, 3.5, and 3.2 kilobases (kb). There was an additional

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band at 6.0 kb that usually was faint but in the case of C57BL/6 DNA in this gel it was strong. This band was shown to arise from partial digestion (see next section). The 3.5- and 4.8-kb bands represent V\(_A\) and V\(_\lambda\) genes, respectively, as reported (19). The V\(_A\) gene was detected by its established cross-hybridizability (19) with the V part of the (V + C)\(_\lambda\) probe. The amino acid sequence of C\(_\lambda\) and C\(_\lambda\) differs by only five residues between position 120 and the carboxy terminus (11), and we therefore expected to detect the C\(_\lambda\) and C\(_\lambda\) genes with the (V + C)\(_\lambda\) probe. On the other hand, C\(_\lambda\) and C\(_\lambda\) proteins differ by approximately 30 amino acids of 94 (11) and we would not expect cross-hybridization. Therefore, the two bands at 8.6 and 3.2 kb seen with the (V + C)\(_\lambda\) probe are likely candidates for the C\(_\lambda\) and C\(_\lambda\) genes.

The C\(_\lambda\) probe (Fig. 1B) revealed one major band at 8.6 kb, known to contain the C\(_\lambda\) gene (19), and another band at 2.8 kb, seen previously (13) but not characterized. The band at 2.8 kb did not cross-hybridize with the (V + C)\(_\lambda\) probe (Fig. 1A) and therefore does not contain the C\(_\lambda\) gene and also probably not the C\(_\lambda\) gene. It possibly represents a new C\(_\lambda\) gene which we tentatively refer to as C\(_\lambda\). The partial band at 6 kb as well as the band at 8.6 kb hybridized with both probes and will be further described below.

**Clones of the 8.6-, 6.0-, and 2.8-kb DNA Fragments.** The 8.6-, 6.0-, and 2.8-kb fragments were enriched by preparative gel electrophoresis and cloned in AWES phage. A Southern blot of the phage DNA of these three types of clones, Ig16.30, Ig10A1, and Ig16.E5, is shown in Fig. 2. Clone Ig16.30, containing an 8.6-kb EcoRI fragment and selected by hybridization with (V + C)\(_\lambda\), was found to be identical with our previous C\(_\lambda\) clone, Ig25A (19), based on restriction enzyme digestion and heteroduplex formation (data not shown). Both clones also hybridized with the (V + C)\(_\lambda\) and C\(_\lambda\) probes. When Ig25A DNA was cleaved with both EcoRI and Kpn I, the 1.5-kb fragment on the 5' side of this clone (4) hybridized with the (V + C)\(_\lambda\) but not the C\(_\lambda\) probe. The 3.4- and 3.8-kb fragments hybridized with C\(_\lambda\), as predicted from previous restriction map analysis (3), but did not hybridize with (V + C)\(_\lambda\). Because the Ig25A clone does not contain V sequences (19), these results suggested that this insert carried either the C\(_\lambda\) or C\(_\lambda\) gene in addition to the C\(_\lambda\) gene (see next section).

Clone Ig10A1, although derived from the 6-kb region of the agarose gel, produced two fragments of 3.2 and 2.8 kb upon complete EcoRI digestion (Fig. 2A). The 3.2-kb fragment hybridized with (V + C)\(_\lambda\) (Fig. 2C) but not with the C\(_\lambda\) probe (Fig. 2B) or V(I)\(_\lambda\) (data not shown), suggesting that this fragment contains either the C\(_\lambda\) or C\(_\lambda\) gene. The other EcoRI fragment of this clone, at 2.8 kb, hybridized with the C\(_\lambda\) probe but not with the (V + C)\(_\lambda\) probe and is indistinguishable from the 2.8-kb insert of clone Ig16.E5 containing the C\(_\lambda\) gene. Thus, clone Ig10A1 also carries two CA genes: C\(_\lambda\) or C\(_\lambda\) on the 3.2-kb fragment and C\(_\lambda\) on the 2.8-kb fragment. This conclusion is also supported by the fact that the weak band at 6 kb in Ig10A1, representing the partial digestion, hybridized with both the (V + C)\(_\lambda\) and C\(_\lambda\) probes. Another distinct clone, Ig3S, derived from a library of an EcoRI partial digest, contained a 1.5-kb EcoRI fragment hybridizing with C\(_\lambda\) but not (V + C)\(_\lambda\). This clone has not been characterized further.

**Identification of J\(_3\) and C\(_3\) Segments and Their Linkage to J\(_1\) and C\(_2\) Segments.** Fig. 3 A and B shows electron micrographs of hybrids formed between the double-stranded 8.6-kb EcoRI insert of Ig25A and a mixture of \(A_1\) and \(A_2\) or \(A_1\) and \(A_2\) mRNAs, respectively. The position of the C\(_\lambda\) gene in Ig25A has been previously determined to be 3.9 kb from the 3' EcoRI end (19). The \(A_1\) plus \(A_1\) mRNA gave a small R loop 0.6 kb from one end and a larger loop 3.9 kb from the other end. In some molecules the larger loop accompanied a 1.3-kb double-stranded DNA loop. We conclude that the larger loop is due to hybrid formation between \(A_1\) mRNA and the C\(_\lambda\) gene, based on its position from the EcoRI ends. The 1.3-kb loop is due to hybridization of \(A_1\) mRNA to the J\(_1\) DNA segment (19). The other R loop must be due to hybridization of \(A_2\) mRNA to the second CA gene because, as established (19), \(A_1\) mRNA does not give an R loop at this position. A mixture of \(A_2\) and \(A_1\) mRNA also gave the double R-loop structure similar to the one obtained.
mRNA with the 5' CA gene. We therefore conclude that the 5' CA gene is CA3 rather than CA2 and that Ig25A carries both the λ3 and λC gene segments.

In order to determine if the CA3 gene also had its J1 to its 5' side, we screened a library of an EcoRI partial digest of BALB embryo DNA. IgS6.2 is a representative clone containing a 5-kb fragment to the 5' side of the 8.6-kb EcoRI fragment of clone Ig25 (Fig. 2). Fig. 3D shows the RNA-DNA hybrid structure obtained when single-stranded IgS6.2 DNA was hybridized with λ2 and λ1 mRNA. The λ1 mRNA, used as a marker, hybridized to JA1 and CA1 separated by the 1.3-kb intron which appeared as a single-stranded DNA loop. The λ2 mRNA hybridized with the CA3 gene and also with a short DNA segment located 1.3 kb 5' to it, giving rise to a 1.3-kb single-stranded DNA loop. We interpret this short DNA segment as JA3. The hybrid structure shown in Fig. 3D also indicates that the two CA genes are oriented in the same 5'-to-3' direction because the two mRNAs hybridized with the same DNA strand. Fig. 3E summarizes the positions of the various λ gene segments on IgS6.2.

**Linkage of JA3, CA2, and JA1, CA1 Gene Segments.** In order to determine that clone Ig10A1 carried the CA2 gene, we made R loops of double-stranded EcoRI-digested DNA with either λ2 (Fig. 4A) or λ3 (Fig. 4B) mRNA. The large open loops of the 3.2-kb fragment with λ3 mRNA compared with the smaller loops with λ3 mRNA indicated that this gene was indeed CA3, supporting our previous assignment of the CA3 gene to the 5.6-kb fragment. The hybrid formed between the 3.2-kb single-stranded DNA fragment and λ2 mRNA gave a structure characteristic of the J and C DNA segments, the JA1 segment being 1.4 kb 5' to the CA3 gene (Fig. 4C). Hybridization of λ2 mRNA to the JA1 DNA segment is also indicated in the left side of Fig. 4A by the 1.4-kb double-stranded DNA loop. When λ1 mRNA was used, only the 2.8-kb fragment gave the similar structure, but at a lower frequency (Fig. 4D). A DNA-RNA hybrid of about 400 bp with a 1.3-kb DNA loop was found 0.8 kb from one (5') end and 0.3 kb from the other (3') end. Therefore, CA1 also carries its own J.

To determine the relative position and orientation of the CA2 and CA1 genes, λ1 and λ2 mRNAs were hybridized individually or as a mixture with clone Ig10A1 DNA partially digested with EcoRI. The λ2 mRNA often gave a hybrid 0.5 kb from one (5') end of the 6-kb fragment; occasionally the λ1 mRNA also showed a hybrid 0.3 kb from the opposite (3') end (Fig. 4E). In this manuscript, JA1 is not seen because of weak homology of λ1 mRNA with the λ3 gene. The distance between the CA1 and CA3 genes is 3.0 kb, similar to that between CA3 and CA1 (Fig. 3E). The positions of the various gene segments on the 6.0-kb insert of Ig10A1 are shown in Fig. 4F.

**A Chain SharesVA1 Gene With λ1 Chain.** The CBPC49 λA myeloma (11) DNA gave a characteristic rearranged band at 2.8 kb when analyzed by using the V(λ) probe (Fig. 1C). The size of this rearranged fragment is compatible with joining of VA to JA1. The distance from the 5' EcoRI site to the VA1 segment is 1.65 kb (19). Because the complete V gene is about 0.5 kb and the distance from JA3 to the 3' EcoRI site is 0.65 kb (Fig. 3), the expected fragment size of VAJ3 would be about 2.5 kb (1.65 + 0.5 + 0.65). In contrast, joining of VA1 (22) to JA3 would not explain the 2.8-kb fragment observed in the λA myeloma because it would have produced a 4.5-kb (3.3 + 0.5 + 0.7) fragment.

To demonstrate directly that VA1 is joined with JA3 in the λA myeloma, we cloned and characterized the 2.8-kb fragment (clone Ig284). Electron micrographs of R loops formed between EcoRI-digested Ig284 and λ3 mRNA showed a single loop of about 380 bp with an RNA tail of 350 bp (Fig. 5A). An identical
structure was seen with $\lambda_3$ mRNA (data not shown). The placement of this V DNA segment 1.7 kb from the 5′ EcoRI site is consistent with its being $\text{VA}_1$ (19). This idea was confirmed by heteroduplex formation of Ig284 DNA with Ig99 [carrying $\text{VA}_1$ and its flanking sequences (19)], which showed that the entire 1.9-kb region extending from the 5′ EcoRI site to the V gene is completely homologous (Fig. 5B). In order to determine whether the rearranged $\text{VA}_1$ gene is connected to $\lambda_3$ heteroduplex formation of Ig284 with Ig66.2 (Fig. 5C), shown above to contain $\text{JA}_3$ and $\text{CA}_3$, was performed in the presence of $\lambda_3$ mRNA. The 0.65-kb duplex was observed immediately 3′ to the $\text{VA}_1$ gene which had been marked by hybridization of the premixed $\lambda_3$ mRNA. The DNA duplex corresponds to the area bounded by $\lambda_3$ and its nearest 3′ EcoRI site. We conclude that the $\text{VA}_1$ segment has joined with $\text{JA}_3\text{CA}_3$ to produce the $\lambda_3$ gene active in the CBPC49 myeloma.

**DISCUSSION**

We have described four C region genes for mouse $\lambda$ light chain immunoglobulins, which occur in two clusters, $\text{J}_{\lambda}\text{C}_3\text{J}_4\text{C}_4$ and $\text{J}_{\lambda}\text{C}_2\text{J}_4\text{C}_4$. Only three $\lambda$ chains have been described to date and therefore we have no information on the function or expression of the $\text{CA}_4$ gene. We also do not know if a fifth $\lambda$ hybridizing segment (in clone IgS3) carries a J segment and if it is functional. Because of cross-hybridization between $\text{CA}_1$ and $\text{CA}_4$ and between $\text{CA}_3$ and $\text{CA}_4$, we suggest that there was an evolutionary precursor, $\text{CA}_1$, for $\text{CA}_1$ and $\text{CA}_4$ and a precursor $\text{CA}_{12}$ for $\text{CA}_3$ and $\text{CA}_4$ which duplicated in the unit $\text{J}_{\lambda}\text{C}_1\text{J}_{\lambda}\text{C}_1$ to give the current gene organization. The conserved 3-kb distance between the $\text{CA}_3$ and $\text{CA}_4$ genes and between the $\text{CA}_1$ and $\text{CA}_4$ genes is consistent with this idea.

We can derive a probable organization of the $\text{VA}_1$ genes. There seems to be only two V genes, $\text{VA}_1$ and $\text{VA}_2$, used for the $\lambda_1$, $\lambda_2$, and $\lambda_3$ subtypes (refs. 19, 23, and 24, and this paper). The $\lambda_3$-producing myeloma MOPC315 has two nonembryos (rearranged) bands detected by the V(J)$\lambda_1$ probe (Fig. 1C). One band (7.4-kb) is shared with the $\lambda_3$-producing myeloma J558 and M104E (Fig. 5) and is most likely the (V + C)$\lambda_1$ rearranged band because it has been shown that MOPC315 also produces a chain in which amino acid position 30 of $\text{VA}_1$ is joined directly with $\text{CA}_4$ (25). The other band (6.4-kb) is unique for the $\lambda_3$-producing myeloma and is thought to be (V + C)$\lambda_2$. The size of this putative (V + C)$\lambda_2$ fragment in M315 is compatible with a joining of $\text{VA}_2$ to the $\text{CA}_4$ gene: the distance from the 5′ EcoRI site to the $\text{VA}_2$ gene site [clone Ig13 (25)] is 3.3 kb, the complete $\text{V}$ gene is about 0.5 kb, and the distance of $\text{VA}_2$ to the 3′ EcoRI site (clone Ig10A1) is 2.7 kb (Fig. 4F), producing a rearranged fragment of about 6.5 kb, as found in MOPC315. Therefore, MOPC315 has rearranged one copy each of $\text{VA}_1$ and $\text{VA}_2$ and yet maintains both 3.5-kb $\text{VA}_1$ and 4.8-kb $\text{VA}_2$ embryo DNA fragments (Fig. 1C). Because V-J joining almost surely occurs by deletion of the DNA segments between V and J (13, 26), we may rule out an organization of $\text{VA}_1$ and $\text{VA}_2$ in which there is no intervening CA gene. If, for example, the order were $\text{V}_2\text{V}_1$ in the germ-line genome, then $\text{V}_1\text{J}_2\text{V}_2$ joining would have deleted $\text{V}_1$ on one chromosome, and the $\text{V}_1$ rearrangement on the other chromosome would also have removed this $\text{V}$ gene from the germ-line configuration; the 3.5-kb $\text{VA}_1$ band should then have been absent from MOPC315. The analogous argument applies for the 4.8-kb $\text{V}_2$ band if the order were $\text{V}_2\text{V}_1$. Therefore, barring any as yet unknown mechanisms for V rearrangement, such as sister-chromatid exchange, we may tentatively rule out V gene clustering. Because we now know that $\text{VA}_1$ may be used with $\text{JA}_3\text{CA}_4$ in the CBPC, $\lambda_3$-producing myeloma (Fig. 5), and amino acid sequence results of CBPC49 (27), as well as with $\text{JA}_3\text{CA}_1$, the most probable gene order for the $\lambda$ light chains is: $\text{V}_1\text{J}_{\lambda}\text{C}_3\text{J}_4\text{C}_4$ and $\text{V}_1\text{J}_{\lambda}\text{C}_2\text{J}_4\text{C}_4$. This is without knowl-
edge of the organization of one gene cluster to the other except we know that VA1, VA2, and CA1 all are located on chromosome 16 (28). The proposed organization of V and C genes for λ might explain the fact that, in λ chains, V1 has been found only with C1 and C2 and V2 with C3 (11). We would predict that if the C4 gene is functional, it will use V2. The V1 gene may not be efficiently used with C4 nor, likewise, V2 with C3 simply because the distance between these combinations is too great.

Previous data from restriction enzyme mapping of total cellular DNA (19) strongly suggested that there was only one copy per haploid genome of the DNA segment encoding the VA1 and VA2 regions. The absence of the VA1 band (3.5 kb) in J558 (Fig. 6) confirms the point that there is only one VA1 gene per haploid genome. Both copies of the VA1 gene have rearranged in J558: one normally to J1C1 (at 7.4 kb) to produce the λ1 chain, and one nonproductively to J2C3 (at 2.8 kb) (unpublished data). This knowledge of the presence of only one VA1 gene, coupled with the amino acid sequence data of λ1 myeloma proteins showing multiple VA1 sequences (8, 29), again argues that the diversity in myeloma V regions must have been generated somatically.

It has been shown that there is one gene each for CA1 (19) and CA2 and the two C genes share the same V gene, and yet the level of expression of the λ1 gene is much higher than that of the λ2 gene. One obvious possible site for regulation of the expression of these two λ subtype genes is the DNA sequence at or around JA1 and JA2. We propose that a "recombinase" for joining of V1 to J3 or J1, either prefers the J1 region or that mistakes in V-J joining are more often made between V1 and J1 than between V1 and J3. In fact, the 2.8-kb fragment of the J558 myeloma seems to arise by aberrant V1-J3 joining (unpublished data). A genetic defect causes a low level of λ1 chains in the mouse strain SJL. It was previously proposed (30) that this defect may be due to faulty V1-J3 joining; because the structural gene products were not affected, it looked like a single gene defect and the effect was cis-dominant. Thus, in some cases the unequal expression of λ subtype genes may be directly related to the putative sequence signals at or near the J segments.

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