Proc. Natl. Acad. Sci. USA
Vol. 74, No. 2, pp. 716–720, February 1977
Immunology

Amino acid sequence of the NH_2-terminal extra piece segments of the precursors of mouse immunoglobulin λ_1-type and κ-type light chains

(translation of immunoglobulin light chain mRNA/sequence of cell-free protein product/antigen-recognizing receptor/secretory proteins)

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Communicated by Michael Sela, November 10, 1976

ABSTRACT **The mRNA molecules coding for mouse immunoglobulin light (L) chains direct the cell-free synthesis of precursors in which extra peptide segments precede the amino termini of the mature proteins. The results of amino acid sequence analyses of two precursors labeled with 20 radioactive amino acids enabled unambiguous determination of the complete primary structure of the extra piece segments. The complete sequences (and sizes) of the NH_2-terminal extra pieces are: in MOPC-104E λ_1 L-chain precursor, Met-Ala-Trp-Ile-Ser-Leu-Ile-Leu-Ser-Leu-Leu-Ala-Leu-Ser-Ser-Gly-Ala-Ile-Ser (19 residues); in MOPC-41 κ L-chain precursor, Met-Asp-Met-Arg-Ala-Pro-Ala-Gln-Ile-Phe-Gly-Phe-Leu-Leu-Leu-Leu-Phe-Pro-Gly-Thr-Arg-Cys (22 residues). The extra pieces in the precursors of MOPC-104E (λ_1), MOPC-41 (κ), and MOPC-321 (κ) L-chains differ extensively from each other in their amino acid sequence (65–73%). In addition to this sequence heterogeneity, the extra pieces are characterized by a high percentage of hydrophobic residues: 69% in the MOPC-104E λ_1 L-chain precursor (this report), 73–75% in the κ L-chain precursors [Schechter, I. & Burstein, Y. (1976) *Proc. Natl. Acad. Sci. USA* 73, 3273–3277]. The marked hydrophobicity of the extra piece suggests that it may favor interaction of the precursor with cell membranes, in a manner similar to the function of the "hydrophobic domain" of membrane-bound proteins. We propose two possible targets for interaction: (*i*) the endoplasmic membranes, where the NH_2-terminal extra piece is cleaved from the precursor to yield mature protein destined for secretion; (*ii*) the cell surface membrane, where the intact precursor is anchored by virtue of the hydrophobic extra piece to serve as the antigen-recognizing receptor.**

The mRNA molecules coding for a variety of mouse immunoglobulin light (L) chains program *in vitro* the synthesis of precursors larger than the mature L-chains (reviewed in ref. 1). The partial amino acid sequences of several radioactively labeled κ-type (1) and λ_1-type (2) L-chain precursors have shown that in these molecules extra peptide segments (19–22 residues long) precede the amino terminus of the mature protein. The results also indicated that an additional extra piece may be coupled to the carboxy terminus of the L-chain (3). NH_2-Terminal extra pieces have also been identified in prehormones (reviewed in ref. 4) and precursors of pancreatic proteins (5), some of which have been partially sequenced (4–6). The precursors seem to be the immediate product of mRNA translation within the cells (1, 7), and the study of precursors may provide a means to gain new information on the structure and controlled expression of the genes. Partial sequence data of several Ig L-chain precursors were sufficient to provide evidence that: (*i*) the gene coding for the variable (V) region may be larger than hitherto known (8); (*ii*) duplication of a short DNA segment has occurred in the structural gene coding for the MOPC-321 L-chain precursor (9); (*iii*) translation of the L-chain mRNA may be contingent on the NH_2-terminal extra piece, which presumably contains the initiator methionine residue (1, 10); (*iv*) the enzyme(s) converting the precursor to the mature protein (cleavage of the extra piece) may participate in the regulation of L-chain secretion (1); (*v*) the <Glu that blocks the amino terminus of the MOPC-104E λ_1 L-chain is not the initiator residue for synthesis of the L-chain (2), and it has been recently established that the <Glu residue originates from glutamine (Burstein and Schechter, unpublished data).

It was proposed that the modified NH_2-termini of L-chain precursors may serve as a signaling device to direct polysomes synthesizing L-chains to the endoplasmic membranes (11, 12). The early findings on the hydrophobic nature of the NH_2-terminal extra piece (13) support this hypothesis. Some understanding of the functions of the precursors and their presumed interaction with membranes (4–6, 9–12) may be afforded by determination of their structure. We here report the complete primary structures of the NH_2-terminal extra pieces of the precursors of M-104E (λ_1) and M-41 (κ) L-chains.

MATERIALS AND METHODS

The MOPC-104E (M-104E) and MOPC-41 (M-41) mouse myelomas, which produce, respectively, λ_1-type and κ-type L-chains, were kindly donated by M. Potter (National Institutes of Health, Bethesda, Md.).

[^{3}H]Val (15.3 Ci/mmol), [^{3}H]Ile (26 Ci/mmol), [^{3}H]Ser (15 Ci/mmol), [^{3}H]Phe (15.8 Ci/mmol), [^{3}H]Tyr (22 Ci/mmol), [^{3}H]Gln (26 Ci/mmol), [^{3}H]Lys (18 Ci/mmol), [^{3}H]Arg (16.7 Ci/mmol), and [^{3}H]His (55 Ci/mmol) were from the Radiochemical Centre, Amersham, United Kingdom. [^{3}H]Thr (2.1 Ci/mmol), [^{3}H]Trp (20 Ci/mmol), [^{3}H]Asp (23.7 Ci/mmol), [^{3}H]Glu (16.2 Ci/mmol), [^{14}C]Gly (92 mCi/mmol), and [^{35}S]cystine (58 Ci/mmol), were from New England Nuclear, Mass. [^{3}H]Asn (13 Ci/mmol) was from Schwarz/Mann, N.Y. The [^{35}S]cystine was reduced to [^{35}S]cysteine (9).

Immunoglobulin (Ig) L-Chain mRNAs. The mRNA molecules coding for the M-104E λ_1 L-chain (2) and M-41 κ L-chain (8) have been previously characterized. These mRNAs were prepared from myeloma polysomes specifically precipitated by antibodies to the L-chain (13, 14).

Cell-Free Synthesis of L-Chain Precursors. Translation of the L-chain mRNAs was carried out in the wheat germ cell-free system (15) at 25° for 4 hr (1).

Amino Acid Sequence Analyses. The total cell-free products that were labeled by one radioactive amino acid at a time were analyzed in the Beckman model 890C automatic sequencer as detailed elsewhere (10). All samples were sequenced twice. In the duplicates the patterns of radioactive peaks were identical.

Abbreviations: Ig, immunoglobulin; L-chain, immunoglobulin light chain; <Glu, pyroglutamic acid; V-region, variable region; MOPC-321, MOPC-104E, MOPC-63, and MOPC-41 myelomas are abbreviated to M-321, M-104E, M-63, and M-41, respectively.

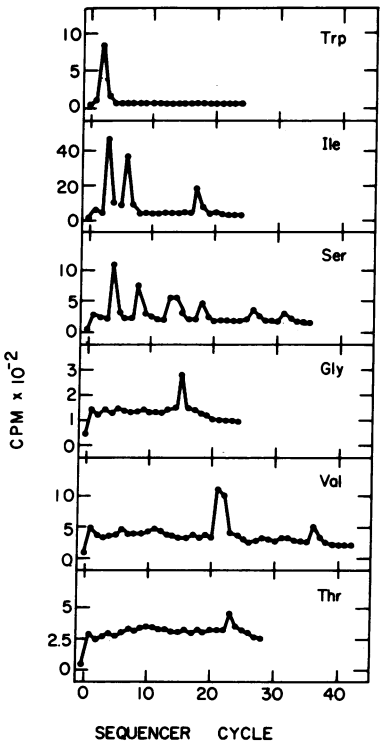

FIG. 1. Radioactivity recovered at each sequencer cycle from the total cell-free products programmed by M-104E λ_1 L-chain mRNA. The products were labeled with the following radioactive amino acids (numbers in parentheses represent cpm in the sample analyzed): [^{3}H]Trp (15,200), [^{3}H]Ile (83,000), [^{3}H]Ser (46,000), [^{14}C]Gly (13,400), [^{3}H]Val (56,000), [^{3}H]Thr (54,600). Background radioactivity obtained from sequencer run of the control sample was subtracted. The control sample consisted of wheat germ extract containing each of the labeled amino acids, but without added mRNA (10). Cycle zero represents a blank cycle (without phenyl isothiocyanate) which was used to wash out potential radioactive contaminants.

The absolute yields (10) of the M-104E λ_1 precursor ranged between 67 and 79%, with the exception of [^{3}H]Trp-labeled precursor, for which the yield was 43%. The absolute yields of the M-41 κ precursors ranged between 63 and 87%.

RESULTS

Sequence Analyses of the Precursor of M-104E λ_1 L-Chain. Analyses of the M-104E L-chain precursor labeled with [^{3}H]Ala, [^{3}H]Leu, [^{3}H]Pro, [^{35}S]Met (2), [^{3}H]Gln, and [^{3}H]Glu (Burstein and Schechter, unpublished data) have shown that the NH_2-terminal extra piece of the precursor is 19 residues long, and that it contains: one methionine at the amino terminus; three alanines at positions 2, 12, and 17; five leucines at positions 6, 8, 10, 11, and 13; and no proline, glutamine, or glutamic acid. The alanine and leucine residues were recovered in high yields (about 95%). On the other hand, the recovery of the amino terminal methionine was rather low (about 10%); presumably this is the initiator methionine, which has been shown to be short lived and rapidly cleaved in other proteins as well (16). Accordingly, 90% of the precursor molecules lacked the amino terminal methionine, and the sequence of the mature L-chain was identified after 18 degradation cycles (2).

In order to determine the entire primary structure of the extra piece, we have synthesized and sequenced M-104E L-chain precursors labeled with the remaining 14 amino acids. Flat and low backgrounds of radioactivity were obtained from sequencer runs (24 cycles) of precursors labeled with [^{3}H]Asp, [^{3}H]Asn, [^{3}H]Phe, [^{3}H]Tyr, [^{3}H]His, [^{3}H]Lys, [^{3}H]Arg, and [^{35}S]cysteine, thus showing that these amino acids are not present in the extra piece of the M-104E L-chain precursor. Results from sequence analyses of precursors labeled with the other six amino acids (Fig. 1) showed radioactive peaks at the indicated degradative cycles: [^{3}H]Trp, cycle 2; [^{3}H]Ile, cycles 3, 6, and 17; [^{3}H]Ser, cycles 4, 8, 13, 14, 18, 26, and 31: [^{14}C]Gly, cycle 15; [^{3}H]Val, cycles 21, 22, and 36; [^{3}H]Thr, cycle 23. In agreement with previous analyses (2), here again after 18 degradative cycles the positions of amino acids in the precursor show perfect homology with the positions of these residues in the mature L-chain. That is, Val^{21}, Val^{22}, Thr^{23}, Ser^{26}, Ser^{31}, and Val^{36} in the precursor match with Val^3, Val^4, Thr^5, Ser^8, Ser^{13}, and Val^{18} in the mature M-104E L-chain (17, 18). Evidently, the extra piece contains one tryptophan, three isoleucines, five serines, one glycine, and no valine or threonine.

The positions of all residues in the precursor of the M-104E L-chain determined here and in earlier studies are given in Fig. 2. Residues in the precursor are numbered assuming that it has an amino terminal methionine (2).

Sequence Analyses of the Precursor of M-41 κ L-Chain. We have previously determined the positions of all hydrophobic residues in the M-41 extra piece (9), by analyzing M-41 precursor molecules that were labeled with the following 11 radioactive amino acids: Met, Leu, Pro, Ile, Ala, Cys, Thr, Phe, Val, Tyr, and Trp. These studies showed that the M-41 mRNA directs the synthesis of two precursors in which 22 or 20 amino acid residues precede the amino terminus of the mature L-chain. About 75% of the molecules have a long extra piece (22

MOPC-104E	Mature	<Glu-Ala-Val-Val-Thr- (1–5)
	Precursor	Met-Ala-Trp-Ile-Ser-Leu-Ile-Leu-Ser-Leu-Leu-Ala-Leu-Ser-Ser-Gly-Ala-Ile-Ser-Gln-Ala-Val-Val-Thr- (1–20)
MOPC-41	Precursor	Met-Asp-Met-Arg-Ala-Pro-Ala-Gln-Ile-Phe-Gly-Phe-Leu-Leu-Leu-Leu-Phe-Pro-Gly-Thr-Arg-Cys-Asp-Ile-
	Mature	Asp-Ile- (1)
MOPC-104E	Mature	Glx-Glx-Ser-Ala-Leu-Thr-Thr-Ser-Pro-Gly-Glx-Thr-Val-Thr-Leu-Thr- (10–20)
	Precursor	Gln-Glu-Ser-Ala-Leu-X-X-Ser-Pro-X-Glu-X-Val-X-Leu-X- (25–40)
MOPC-41	Precursor	Gln-Met-Thr-Gln-Ser-Pro-Ser-Ser-Leu-X-
	Mature	Gln-Met-Thr-Gln-Ser-Pro-Ser-Ser-Leu-Ser- (5–10)

FIG. 2. Alignment of the NH_2-terminal amino acid sequence of the mature and precursor forms of the M-104E λ_1 L-chain and M-41 κ L-chains. The primary structures of the precursors are based on radioactive sequence analyses of precursor molecules programmed by L-chain mRNAs in the wheat germ cell-free system. Data for M-104E λ_1 precursor are from this report and ref. 2; for M-41 κ precursor, from this report and refs. 8 and 9. Sequences of the mature L-chains are from refs. 17 and 18 for M-104E; from ref. 19 for M-41. X in the precursor indicates a position in which the amino acid residue was not identified. <Glu, pyroglutamic acid.

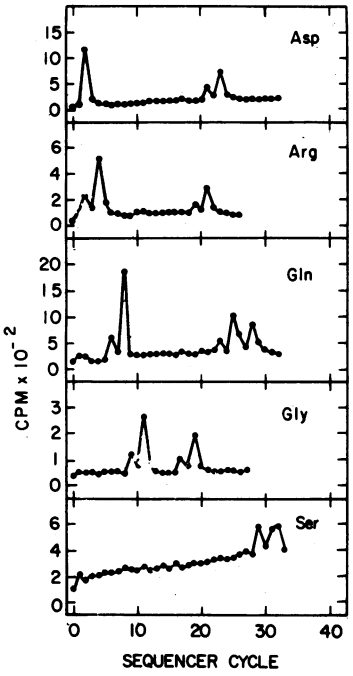

FIG. 3. Radioactivity recovered at each sequencer cycle from the total cell-free products programmed by M-41 L-chain mRNA. The products were labeled with the following radioactive amino acids (numbers in parentheses represent cpm in the sample analyzed): [^{3}H]Asp (41,000), [^{3}H]Arg (12,200), [^{3}H]Gln (57,000), [^{14}C]Gly (17,300), [^{3}H]Ser (83,000). Data were corrected and are presented as detailed in the legend to Fig. 1.

residues), the remaining molecules have a shorter extra piece (20 residues). The two NH_2-terminal residues in the long extra piece are missing in the short extra piece, in the other 20 positions both extra pieces have identical sequences.

In order to determine the entire primary structure of the extra pieces, we have synthesized and sequenced M-41 precursors labeled with the remaining nine amino acids. Sequencer runs (26 cycles) of [^{3}H]Glu-, [^{3}H]Asn-, [^{3}H]His-, and [^{3}H]Lys-labeled precursors yielded only background radioactivity, thus showing that these amino acids are not present in the extra pieces of the M-41 precursors. Results from sequence analyses of precursors labeled with the other five amino acids (Fig. 3) show that the long extra piece (major radioactive peaks) contains: two arginines at positions 4 and 21, one glutamine at position 8, two glycines at positions 11 and 19, one aspartic acid at position 2, and no serine. As expected, the short extra piece (minor radioactive peaks) contains: Arg^2 and Arg^{19}, Gln^6, Gly^9 and Gly^{17}, and no serine or aspartic acid (in the short extra piece the two amino terminal residues of the long extra piece, Met-Asp, are missing). It is also seen that after 22 degradation steps, the sequence of the amino acids in the long precursor shows identity with the sequence of these residues in the mature M-41 L-chain. That is, Asp^{23}, Gln^{25}, Gln^{28}, Ser^{29}, Ser^{31}, and Ser^{32} in the cell-free product (major peaks) match with Asp^1, Gln^3, Gln^6, Ser^7, Ser^9, and Ser^{10} in the mature M-41 L-chain (19). The minor peaks of Asp^{21}, and Gln^{23}, and Gln^{26} that originate from the short precursor (20 residues in the extra piece), also match with the sequence of the mature L-chain.

The positions of all residues in the M-41 precursor having the long extra piece (22 residues) are given in Fig. 2.

DISCUSSION

The samples analyzed contain a minute amount of the labeled precursor (about 0.1 pmol, 2.4 ng) whose sequence is monitored, and a large excess of apomyoglobin carrier (290 nmol, 5 mg). One could envisage difficulties in recovering 0.1 pmol, which is the maximum amount of radioactive amino acid derivative released from the precursor (10). The results, however, were that the radioactivity was recovered in discrete peaks (Figs. 1 and 3). Furthermore, the analyses of each L-chain precursor that was labeled with 20 radioactive amino acids, one at a time, were unambiguously interpreted as distinct sequences of fairly long peptide segments: 29 residues in M-104E (19 of the extra piece plus 10 of the mature L-chain); 33 residues in M-41 (22 of the extra piece plus 11 of the mature L-chain) (Fig. 2). These experiments demonstrate that the amino acid sequence of minute amounts (0.1 pmol) of a highly labeled protein can be faithfully determined in the presence of a large excess (over a millionfold) of unrelated nonradioactive proteins. Radioactive sequence analysis of proteins available in trace amounts was applied in 1973 to study the MOPC-321 (M-321) L-chain precursor (13). This procedure is currently being used to determine the structure of similar NH_2-terminal extra pieces of prehormones (4, 6) and precursors of pancreatic proteins (5), as well as of histocompatibility antigens (20, 21). These studies have provided, so far, only partial sequences. We here report complete primary structures for the NH_2-terminal extra pieces of the M-104E λ_1 and M-41 κ L-chain precursors (Fig. 4).

The NH_2-terminal extra piece is linked to the V-region of the mature L-chain. Sequence data from κ-chain precursors strongly indicate that the extra piece is part of the V-region (1, 8), because in precursors of κ L-chains of different subgroups (M-41 versus M-321 and M-63) the extra pieces differ in size and sequence; in κ precursors of the same subgroup (M-321 and M-63) the extra pieces are of the same size and so far they share an identical partial sequence (Fig. 4). In M-41 and M-321 precursors the extent of sequence variability at the extra piece (at least 68%) is greater than it is in the entire V-region (48%), and it is comparable to the variability found when only the

	Extra piece																				Mature L chain	
	Met	Ala	Trp	Ile	Ser	Leu	Ile	Leu	Ser	—	Leu	Leu	Ala	Leu	Ser	Ser	Gly	Ala	Ile	Ser	MOPC-104E	λ_1
Met-Asp	Met	Arg	Ala	Pro	Ala	Gln	Ile	Phe	Gly	Phe	Leu	Leu	Leu	Leu	Phe	Pro	Gly	Thr	Arg	Cys	MOPC-41(a)	κ
	Met	Arg	Ala	Pro	Ala	Gln	Ile	Phe	Gly	Phe	Leu	Leu	Leu	Leu	Phe	Pro	Gly	Thr	Arg	Cys	MOPC-41(b)	κ
	Met	X	Thr	X	Thr	Leu	Leu	Leu	Trp	Val	Leu	Leu	Leu	Trp	Val	Pro	X	Ser	Thr	X	MOPC-321	κ
	Met	X	X	X	X	Leu	Leu	Leu	X	X	Leu	Leu	Leu	X	X	Pro	X	Ser	X	X	MOPC-63	κ

FIG. 4. Sequence homology between the NH_2-terminal extra pieces of precursors of mouse immunoglobulin L-chains. The complete sequences of the M-104E extra piece (this report and ref. 2) and of the M-41 extra piece (this report and refs. 8 and 9) are based on analyses of precursor molecules labeled with 20 radioactive amino acids. The long (a, 22 residues) and short (b, 20 residues) extra pieces of the two M-41 precursors are given (8). The partial sequence of the M-321 extra piece is based on analyses of precursor labeled with 12 radioactive amino acids (Met, Ala, Val, Leu, Ile, Pro, Thr, Cys, Phe, Tyr, Trp, and Ser, refs. 9 and 10). The partial sequence of the MOPC-63 (M-63) extra piece is based on analyses of precursor labeled with six radioactive amino acids (Met, Ala, Leu, Ile, Pro, and Ser, ref. 1). For maximal homology between the complete sequences of M-104E and M-41 extra pieces, a gap (indicated by a dash) was inserted in the M-104E sequence. Homologous regions between different L-chains are enclosed. X indicates an amino acid whose identity is unknown.

Table 1. Sequence heterogeneity at the NH_2-terminal extra piece of L-chain precursors

Light chain precursors compared*	Amino acid differences in Extra piece No.	%	Variable† region No.	%	Hypervariable† regions No.	%
M-104E (λ_1)/M-41 (κ) (a)	16/22	73	64/110	58	23/30	77
M-104E (λ_1)/M-41 (κ) (b)	14/20	70	64/100	58	23/30	77
M-104E (λ_1)/M-321 (κ)	14/20	70‡	68/111	61	24/31	77
M-321 (κ)/M-41 (κ) (a)	15/22	68‡	53/111	48	20/31	65
M-321 (κ)/M-41 (κ) (b)	13/20	65‡	53/111	48	20/31	65

* (a) and (b) represent M-41 L-chain precursors with the long (22 residues) and short (20 residues) extra pieces, respectively (8).
† Numbers for the entire variable region and for the hypervariable regions (22) are based on sequences of the mature L-chains: M-104E (17, 18), M-41 (19), M-321 (23).
‡ Numbers represent minimal values because they are based on partial sequence of the M-321 extra piece given in Fig. 4.

hypervariable regions (22) of these L-chains are examined (65%) (Table 1). Since the V-regions of Ig chains are coded by distinct genes [other than the constant (C) region genes], it was of interest, and relevance, to compare the κ and λ precursors. The results corroborate our previous findings obtained with κ-precursors (8, 9) concerning the size and sequence variability of the extra piece. The extra piece of the M-104E λ_1 precursor differs extensively in sequence from the extra pieces of the two κ precursors (70–73%), which are quite different from each other (68%) (Table 1). Also the extra piece of the λ_1 precursor (19 residues long) is shorter than that found in the κ precursors (20 and 22 residues long) (Fig. 4). Although the V-regions and hypervariable regions of λ_1 and κ chains differ extensively in sequence, it is seen that the extent of sequence heterogeneity between the extra piece segments of λ_1 and κ (70 and 73%) is somewhat larger than it is between their V-regions (58 and 61%), and it approaches the variability between their hypervariable regions (77%) (Table 1).

The V-regions of mouse κ chains exhibit a high degree (up to 50%) of sequence heterogeneity (23), while the V-regions of the λ chains (17, 18) are extremely uniform in structure (up to 3% heterogeneity). This can be due to a small pool of λ V-genes or to restricted expression of a larger pool of λ V-genes (17, 18).

Table 2. Distribution of hydrophobic residues in immunoglobulin L-chain precursors and membrane-bound proteins

Protein	Hydrophobic/total residues No.	%	No.	%
	Extra piece		Mature L-chain	
M-104E λ_1 precursor	13/19	69	118/215	55
M-41 κ precursor (a)	16/22	73	97/213	46
M-41 κ precursor (b)	15/20	75	97/213	46
M-321 κ precursor	15/20	75	107/218	49
	Hydrophobic domain		Exposed portion	
Glycophorin	17/23	74	60/124	48
Cytochrome b_5	29/40	72	40/97	41

Numbers are calculated from data in: refs. 17, 19, and 23 for the mature L-chains of M-104E, M-41, and M-321, respectively; ref. 9 for the extra pieces of M-41 and M-321; this report for the extra piece of the M-104E λ_1 precursor (Fig. 2); refs. 25 and 26 for glycophorin; ref. 27 for cytochrome b_5.

Clarification of this problem might be achieved by determining the structure of several λ precursors. Evidence supporting the possibility of a larger pool of λ V-genes will be obtained if we find sequence heterogeneity in the extra piece of precursors of λ_1 L-chains which share identical V-regions.

A unique role in the structure of the V-region was assigned to glycine residues because of their steric properties; invariant glycines are present in both κ and λ V-regions (22); and they occur at bends of polypeptide loops of the "basic immunoglobulin fold" (24). In connection with this, it is worthy to note that by introducing a gap in the sequence of the M-104E λ_1 extra piece, the glycine residue (occupying the fourth position from the carboxy terminus) matches with a glycine residue in the M-41 κ extra piece (Fig. 4). It will be interesting to find out whether this position is also occupied by glycine residues in the extra pieces of other precursors. Should this be the case, it would indicate the possibility of some common three-dimensional features of the extra pieces.

The NH_2-terminal extra pieces were found to be quite hydrophobic (9). The percentage of hydrophobic residues in the extra piece (69–75%) and mature L-chain (46–55%) "portions" of the precursor is comparable to that found in the "hydrophobic domain" and exposed portions of membrane proteins (e.g., glycophorin; see Table 2). The complete sequences of the precursors further corroborate this resemblance. No charged residues occur in the "hydrophobic domain" of glycophorin (25). Similarly, the entire extra piece of the M-104E λ_1 precursor and a stretch of 16 amino acids (Ala^5 to Thr^{20}) in the extra piece of the M-41 κ precursor are devoid of any charged residues (Fig. 2). These findings suggest that the role of the hydrophobic extra piece is to favor interaction of the precursor with cell membranes (1), in a manner similar to the function of the "hydrophobic domain" of membrane proteins (25–28). On the basis of this structure–function analogy, we have proposed the following hypothesis (9). The Ig precursor, which seems to be the immediate product of mRNA translation within the cell (1, 10), is the common intermediate for secreted Ig and antigen-recognizing receptor. In plasma cells that synthesize large amounts of antibodies most of the precursor molecules are directed to the endoplasmic membranes, where the extra piece is cleaved to yield mature protein destined for secretion; in lymphocytes that synthesize small amounts of Ig, most of the precursor molecules remain intact, and are anchored via the hydrophobic extra piece in the cell-surface membrane to serve as the antigen-recognizing receptor. We can test this hypothesis by evaluating the capacity of heavy (H) and L-chain precursors to recombine and form 7S Ig molecules with antigen-binding capacity, by searching for precursor molecules in the cell sur-

face, etc. If we find precursor molecules on the surface of bone-marrow-derived (B) or thymus-derived(T) lymphocytes, we shall have to consider the possibility that by virtue of its sequence variability the NH_2-terminal extra piece can also function as a new recognition system.

The authors thank Drs. Ron Zemell and Paul Bornstein for discussions, and Miss Frida Kantor, Mrs. Etty Ziv, and Mrs. Zillah Cohen for excellent assistance. This research was supported by Grant CA20817 from the National Cancer Institute, U.S. Public Health Service.

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