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Nucleotide sequences of 4.5S RNAs associated with poly (A) -containing RNAs of mouse and hamster cells

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ABSTRACT

The nucleotide sequences of 4.5S RNAs associated with poly-(A)-containing RNAs of mouse and hamster cells were determined. These RNAs have 91 to 94 nucleotides, a high content of G (almost 40%) and no modified nucleoside. The 5'-termini are pppG, but the 3'-termini lack uniformity in the number of uridylate residues. These molecules contain two sets of repeating sequences, and a central purine-rich sequence. There is only one base exchange between mouse and hamster 4.5S RNAs. Possible binding sites of these RNAs to poly(A)-containing RNAs are discussed.

INTRODUCTION

Series of 4.5S RNAs have been isolated from Moloney murine leukemia virus (Mo-MuLV), Friend spleen focus forming virus (SFFV), SFFV-infected mouse cells and uninfected mouse, rat and hamster cells (1-3). These molecules are associated with viral genomic RNAs and also with nuclear and cytoplasmic poly(A)-containing RNAs from infected or uninfected cells (1-3). However, no series of 4.5S RNAs was found in human, monkey, cat, mink, rabbit or chicken cells (3). The specific association of these molecules with nuclear and cytoplasmic poly(A)-containing RNAs suggests that they could have an important cellular function(s), such as in splicing of heterogeneous nuclear RNAs (hnRNAs), transportation of mature mRNA from the nucleus to the cytoplasm, translational control of mRNA, or protection of poly-(A)-containing RNAs from nuclease attack. To obtain information on their function(s), we determined the nucleotide sequences of 4.5S RNAs of mouse and hamster cells. These RNAs contain 91 to 94 nucleotides, no modified nucleoside, pppG as the 5'-terminus and various number of uridylate residues at

the 3'-terminus. These 4.5S RNAs are rich in guanylate residues and have a central purine rich sequence.

MATERIALS AND METHODS

Materials. Enzymes were obtained from the following sources : RNases T1, T2 and U2 from Sankyo Co. Ltd.; RNase A and polynucleotide phosphorylase from Sigma Chemical Co.; snake venom phosphodiesterase and bacterial alkaline phosphatase from Worthington Biochemical Corp.; nuclease P1 from Yamasa Shoyu Co.; RNase H from Enzo Biochem. Inc. Silkworm nuclease was a gift from Dr. J. Mukai of Kyushu University. Poly(dA-dG)·poly(dT-dC) was a gift from Dr. S. Nishimura of this institute. Acrylamide and N, N'-methylenebisacrylamide were obtained from Eastman Organic Chemicals. Cellulose acetate (Separax) was a product of Fuji Film Co. DEAE-cellulose thin-layer plates (Polygram Cel 300 DEAE) were purchased from Machery-Nagel.

Purification of ^{32}P-labeled 4.5S RNA. Mouse kidney cells (C3H2K), mouse lymphoma cells (L1210/C) and baby-hamster kidney cells (BHK-21) were labeled for 4 or 24 hours with [^{32}P]phosphate and nucleic acids were extracted as described previously (3). Nucleic acids were dissolved in a solution of 20mM Tris-HCl (pH 7.5), 10 mM NaCl and 1 mM EDTA and then heated at 95°C for 90 sec. The low molecular weight RNA fraction (4 to 7S) was separated from higher molecular weight RNAs in a 5 ml of a gradient of 5 to 20% sucrose in TSE buffer (20mM Tris-HCl, pH 7.5; 0.1M NaCl; 1mM EDTA) in a Beckman SW-50.1 rotor by centrifugation for 3 hours at 50,000 rpm. The low molecular weight RNA fraction was then separated by two dimensional gel (2-D gel) electrophoresis by a modification (2) of the method of Ikemura et al. (4,5). The region of gel containing 4.5S RNA was cut out and subjected to further electrophoresis in 16% polyacrylamide gel containing 7M urea (6), since this gave complete separation of the 4.5S RNA from 4.5S RNA$_I$ (7) and several minor RNAs.

Sequence analysis. Standard procedures (8,9) were used for enzymatic digestion of purified 4.5S RNA, fingerprinting and identification of oligonucleotides from fingerprints. Reaction conditions for nuclease P1, polynucleotide phosphorylase and silkworm nuclease have been described (10-12). The digestion

products with polynucleotide phosphorylase and silkworm nuclease were separated by two dimensional paper electrophoresis (8), and the resulting oligonucleotides were digested with RNase T2 or nuclease P1, and analyzed by two dimensional thin-layer chromatography (13).

Large oligonucleotide fragments of the 4.5S RNA were obtained by partial digestion with RNase T1 (0.01μg plus 50μg of carrier RNA in 3μl of 0.01M Tris-HCl, pH 7.6, and 0.01M $MgCl_2$ for 10 min at 4°). The partial digestion products were purified (14) and their sequences were identified (15).

Large fragments were also obtained by cutting the RNA with RNase H. 4.5S RNA was hybridized to poly(dC-dT), prepared from poly(dA-dG)·poly(dC-dT) by depurination (16), and was digested with RNase H (17). The digestion mixture was fractionated by 2-D gel electrophoresis and purified spots were digested with RNase T1 or RNase A and analyzed by fingerprinting.

RESULTS

Complete RNase T1 and RNase A digestion products of mouse 4.5S RNA. Figure 1a and b show fingerprints of 4.5S RNA from L1210 cells obtained after digestion with RNase T1 and RNase A, respectively. The 4.5S RNA from C3H2K cells gave identical fingerprints to those of L1210 cells (3). For these fingerprints, 5 mM EDTA was included in the buffer in the first dimension, and 5'-terminal oligonucleotides (14, 14', 113 and 113') were resolved from other oligonucleotides (18) better than in previous fingerprints (2,3).

The structure of each oligonucleotide was determined by digestion with various enzymes as indicated in Tables I and II.

The 5'-terminal nucleotide of this RNA was mainly pppG with small amounts of ppG and pG.

The 3'-terminus of this RNA was not uniform (1-3). In the preparation used for Figure 1a, there were four different 3'-terminal oligonucleotides corresponding to 16b through e in reference 3. Analysis of these oligonucleotides by digestion with RNase A showed that the amounts of Cp, A-Cp and A-Up were constant (1,2 and 1 mole, respectively) in each oligonucleotide, but that the amounts of uridylate residues of 16b, c, d, and e

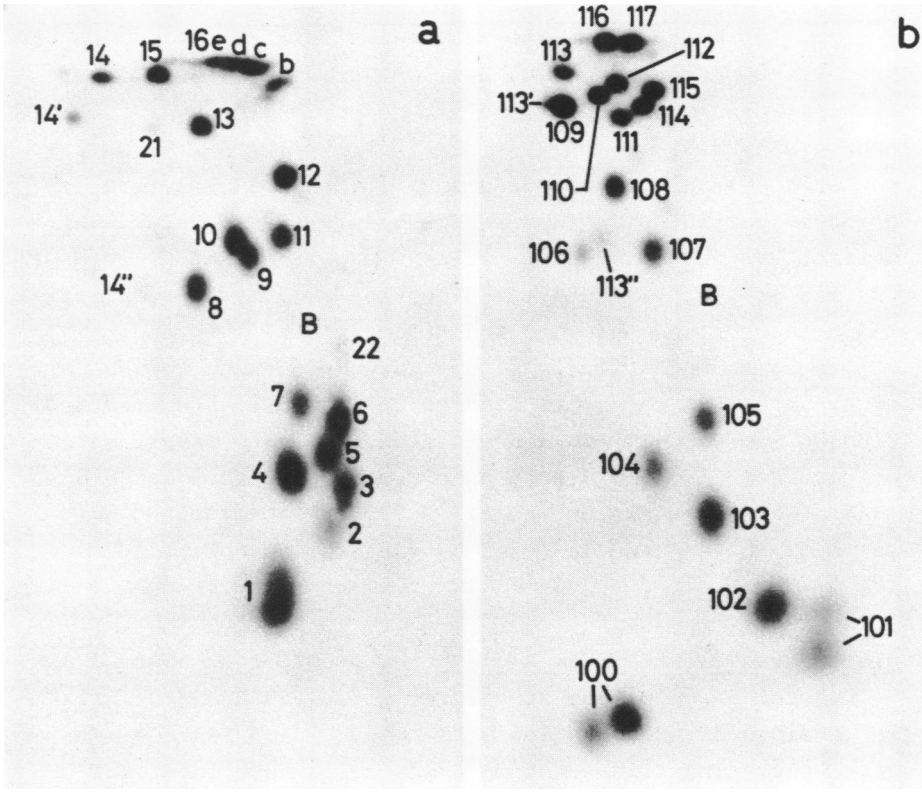


Figure 1. Fingerprints of RNase T1 (a) and RNase A (b) digests of mouse 4.5S RNA. The first dimension, right to left, was electrophresis on cellulose acetate in pyridine acetate(pH 3.5)-7M urea-5 mM EDTA. The second dimension, from top to bottom, was electrophoresis on DEAE-cellulose in 7% formic acid. B denotes the position of the blue dye marker (xylene cyanol FF).

were 2, 3, 4 and 5 moles, respectively. On the other hand, analysis of RNase U2 digestion products showed that each 3'-terminal oligonucleotide contained 2 moles of C-Ap, 1 mole of C-U-Ap and 1 mole of U(pU)n. The n-numbers of U(pU)n from 16b, c, d and e were determined as 2, 3, 4 and 5, respectively by cochromatography with authentic unlabeled U(pU)n on a cellulose thin layer plate with the solvent system of n-propanol-concentrated NH_4OH-H_2O (55:10:35, v/v/v).

Alignment of the oligonucleotides. Large oligonucleotide

Table I. Analysis of RNase T1 End Products

Spot No.	RNase T2 Products	RNase A Products	5'-terminal Nucleoside[a]	Other Digestion Products[b]	Sequence	Molar Yield Measured	Molar Yield Theoretical
1	Gp	Gp			Gp	13.1	13
2	Cp,Gp	Cp,Gp	C		C-Gp	0.8	1
3	2Cp,Gp	2Cp,Gp	C		C-C-Gp	1.6	2
4	Ap,Gp	A-Gp	A		A-Gp	4.6	5
5	Cp,Ap,Gp	Cp,A-Gp	C		C-A-Gp	1.8	2
6	2Cp,Ap,Gp	3Cp,A-Cp,Gp,A-Gp	C	C-Ap,C-C-Ap,Gp,C-Gp(1)	C-C-A-Gp C-A-C-Gp	1.7	2
7	2Ap,Gp	A-A-Gp	A		A-A-Gp	1.0	1
8	Up,Gp	Up,Gp	U		U-Gp	2.4	2
9	Cp,Up,Gp	Cp,Up,Gp	C		C-U-Gp	1.0	1
10	Up,Ap,Gp	Up,A-Gp	U		U-A-Gp	2.3	2
11	2Cp,Up,Gp	2Cp,Up,Gp	C	C-C-U(2)	C-C-U-Gp	0.9	1
12	2Cp,Up,2Ap,Gp	Cp,A-Cp,A-Up,Gp	A	A-U-C(2)	A-U-C-A-C-Gp	1.0	1
13	Cp,2Up,Gp	Cp,2Up,Gp	U	U-U-C(2)	U-U-C-Gp	1.2	1
14	pppGp	pppGp	pppG	pGp(3)	pppGp	0.6	
14'	ppGp	ppGp	ppG		ppGp	0.3	1
14"	pGp	pGp	pG		pGp	0.1	
15	3Up,Ap,Gp	2Up,A-Up,Gp	A		A-U-U-U-Gp	1.2	1
16c[c]	3Cp,4Up,3Ap	Cp,3Up,2A-Cp,A-Up	C	C-U-A,C-U-A-C(4) 2C-Ap,C-U-Ap,U-U-U-U(1)	C-U-A-C-A-C-A-U-U-U-U	1.1[d]	1
21	2Up,Gp	2Up,Gp	U		U-U-Gp	0.1	
22	3Cp,2Ap,Gp	Cp,2A-Cp,Gp	C		C-A-C-A-C-Gp	0.1	

The ratios of yields of redigestion products are shown to the nearest integer (within 15% of the calculated values, in all cases). [a] The 5'-terminus of each oligonucleotide was determined by nuclease P1 digestion. [b] Other digestions which were performed were as follows : (1), RNase U2;(2), Polynucleotide phosphorylase;(3), Venom phosphodiesterase;(4), Silkworm nuclease. [c] Sequence data on oligonucleotide 16c are shown as representative of the 3'-terminal oligonucleotides of the 4.5S RNA. [d] Total of the 3'-terminal oligonucleotides.

Table II. Analysis of RNaseA End Products

Spot No.	RNase T2 Products	RNase T1 Products	5'-terminal Nucleoside[a)]	Other Digestion Products[b)]	Sequence	Molar Yield Measured	Molar Yield Theoretical
100	Up	Up			Up	10.6	7~10
101	Cp	Cp			Cp	6.6	6
102	Cp,Ap	A-Cp	A		A-Cp	3.8	4
103	Cp,Gp	Cp,Gp	G		G-Cp	3.0	3
104	Up,Ap	A-Up	A		A-Up	1.3	1
105	Cp,Ap,Gp	Cp,A-Gp	A		A-G-Cp	1.0	1
106	Up,Gp	Up,Gp	G		G-Up	0.4	
107	Cp,2Gp	Cp,2Gp	G		G-G-Cp	1.0	1
108	Up,Ap,Gp	Up,A-Gp	A		A-G-Up	1.1	1
109	Up,2Gp	Up,2Gp	G		G-G-Up	3.4	3
110	Up,Ap,2Gp	Up,Gp,A-Gp	G		G-A-G-Up	1.2	1
111	Cp,3Gp	Cp,3Gp	G		G-G-G-Cp	0.8	1
112	Up,2Ap,2Gp	Gp,A-Up,A-Gp	A		A-G-G-A-Up	1.2	1
113	Cp,pppGp	Cp,pppGp	pppG	pG,pCp(3)	pppG-Cp	0.6	
113'	Cp,ppGp	Cp,ppGp	ppG		ppG-Cp	0.3	1
113"	Cp,pGp	Cp,pGp	pG		pG-Cp	0.2	
114	Cp,Ap,3Gp	Cp,2Gp,A-Gp	G	G-A-G(2)	G-A-G-G-Cp	1.0	1
115	Cp,2Ap,3Gp	Cp,Gp,2A-Gp	A	A-G-A(2),(4)	A-G-A-G-G-Cp	1.0	1
116	Up,3Ap,4Gp	2Gp,A-Up,2A-Gp	A	A-G-A(2)			
				A-G-A,A-G-A-G,pG-A-Up, pG-G-A-Up(4)	A-G-A-G-G-G-A-Up	1.2	1
117	Cp,3Ap,5Gp	Cp,3Gp,A-Gp,A-A-Gp	G	G-A-A,G-A-A-G-G-A, pG-G-Cp(4)	G-A-A-G-G-A-G-G-Cp	1.0	1

(See footnotes to Table I.)

fragments of the 4.5S RNA were obtained by partial digestion with RNase T1 and by digestion with RNase H. In the latter case, since this RNA contained two -A-G-A-G-sequences, we chose poly-(dC-dT) as the partner of the 4.5S RNA for the RNA-DNA hybrid.

The partial digestion products are summarized in Figure 2, which shows the sequences deduced for the 4.5S RNA. Donis-Keller reported that the recognition structure of RNase H was a hybrid of at least 4 contiguous bases (19). This was also true in this experiment except for nucleotides 62-64: though this sequence contains only 3 contiguous base pairs, RNase H cleaved this sequence fairly well. On the other hand, the second -A-G-A-G-sequence was fairly resistant to digestion by RNase H. This sequence might be involved in the higher structure. A possible secondary sturcture of the 4.5S RNA is shown in Figure 3. There was a submolar amount of oligonucleotide 22(C-A-C-A-C-Gp) in the RNase T1 fingerprint (Fig. 1a, Table I). The partial RNase T1 digestion products contained a small amount of C-A-C-A-C-G-C-C-G-G-U-A-Gp. Therefore, partial base substitution from G to A at position 16 from the 5'-terminus of this RNA must have occurred on the genes for the 4.5S RNA.

The nucleotide sequence of the 4.5S RNA from hamster cells. In a previous paper, we showed that the structures of the 4.5S RNAs from mouse and hamster cells are very similar, but not identical (3). We analyzed the RNase T1 and the RNase A digestion products of the 4.5S RNA from BHK cells and found the following differ-

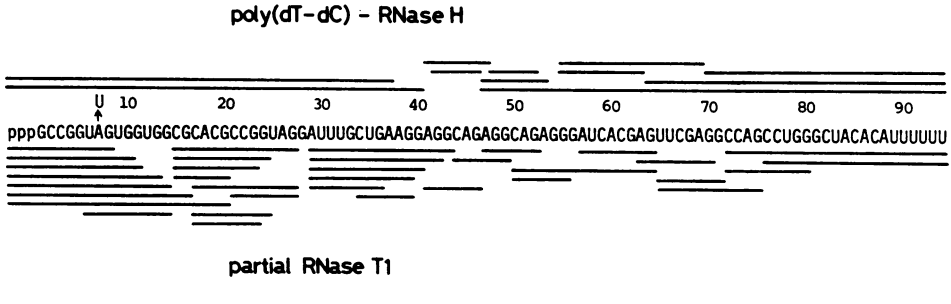


Figure 2. Nucleotide sequence of the 4.5S RNA. The lines above the sequence represent RNase H digestion products. The lines below the sequence represent partial RNase T1 digestion products. The base exchange between mouse(A) and hamster(U) cells at position 7 is shown.

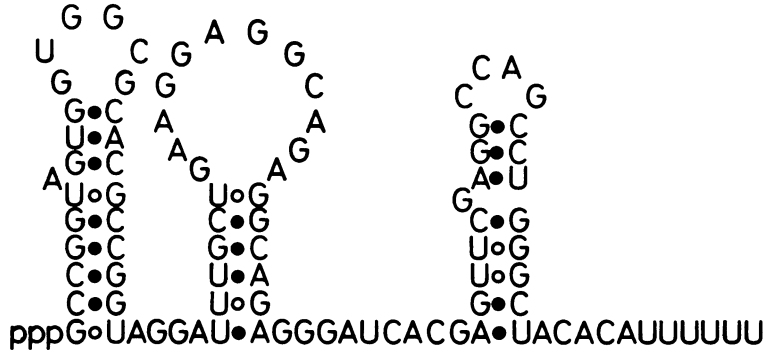


Figure 3. A possible secondary structure of the 4.5S RNA.

ences between mouse and hamster 4.5S RNAs. (i) In the RNase T1 digestion products of mouse 4.5S RNA, there were two moles of U-A-Gp and a small amount of U-U-Gp while in those of hamster 4.5S RNA there were one mole each of U-A-Gp and U-U-Gp. (ii) In the RNase A digestion products of mouse 4.5S RNA there were one mole of A-G-Up and a small amount of G-Up while in those of hamster there was one mole of G-Up and no A-G-Up. (iii) There was no C-A-C-A-C-Gp in hamster 4.5S RNA. Otherwise, the digestion products of these two 4.5S RNAs were qualitatively and quantitatively indistinguishable. Moreover, we obtained pppG-C-C-G-G-U-U-Gp from the partial RNase T1 digestion products of hamster 4.5S RNA. From these results we concluded that in hamster 4.5S RNA, A at position 7 is substituted by U. Since there were submolar amounts of U-U-Gp and G-Up in the digestion products of mouse 4.5S RNA, small amounts of these substituted molecules may also exist in the 4.5S RNA of mouse cells.

DISCUSSION

From the final sequence of the mouse 4.5S RNA the numbers of nucleotides were 36pG, 20pC, 19pA and 16-19pU. Since none of the 4.5S RNAs isolated by Ro-Choi *et al.* from the nuclei of Novikoff hepatoma cells has such a high content of pG (20,21), this 4.5S RNA must be different from their molecules.

The 4.5S RNA contains two sets of repeating sequences: one is G-C-C-G-G-U-A-G (residues 1 to 8 and 20 to 27) and the

other is G-A-G-G-C-A-G-A-G-G (residues 40 to 49 and 46 to 55). In the latter sequence, G-A-G-G is repeated three times with two C-A sequences as spacers.

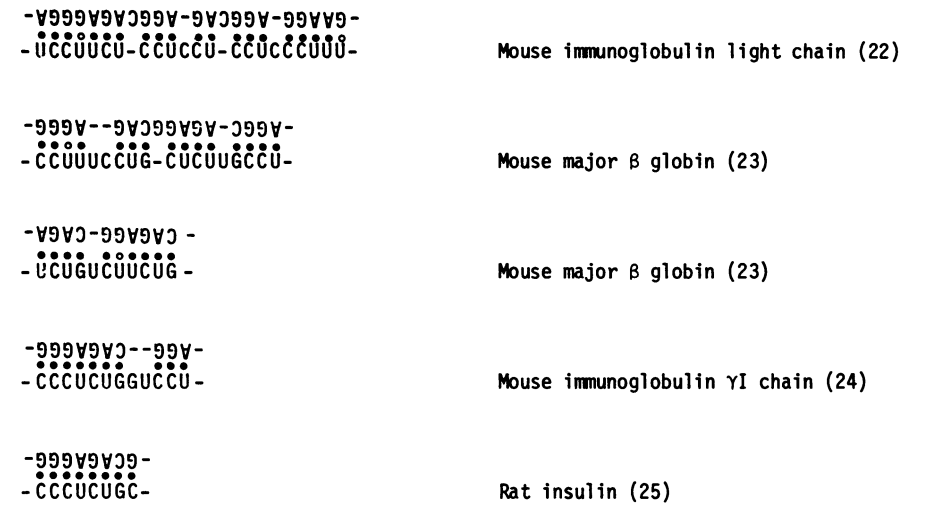
Another striking feature of this molecule is its purine rich sequence : in the center of the molecule, 20 of the 22 nucleotides between positions 36 and 57 are purine nucleotides.

Since this 4.5S RNA is associated with cellular poly(A)-containing RNAs, determination of its binding site(s) on poly(A)-containing RNAs is very important for understanding its function (s). In a preliminary experiment, we found that the purine rich region of the 4.5S RNA hybridized to mouse liver mRNA and was resistant to digestion by a mixture of RNase T1 and RNase A. Many sequences of mRNAs and their genes have now been determined. Most of these primary structures contain pyrimidine rich sequences in their 3'-noncoding regions. Some of them fit very well to the purine rich region of the 4.5S RNA. Other possible binding sites of the purine rich sequence of the 4.5S RNA to poly(A)-containing RNA are the pyrimidine rich regions of the intervening sequences, especially near the 3'-junction of introns. Some possible hybrid structures between the purine rich sequence of the 4.5S RNA and these two pyrimidine rich regions are shown in Figure 4.

Another region of the 4.5S RNA that is less protected from RNase digestion is the region around A-G-C-C-U-G-G-G (residues 74 to 81), which contains the sequence complementary to some of the splice junctions (Table III). Lerner et al. reported that autoantibodies produced by patients with systemic lupus erythematosus (SLE) precipitated nuclear ribonucleoproteins which contain seven small nuclear RNAs (32,33). Since some of the small nuclear RNAs (U1a and U2RNA) contain sequences complementary to splice junctions, they discussed the possibility that these ribonucleoproteins may be involved in the splicing of hnRNAs (33). Since our 4.5S RNA (probably U7RNA of Lerner et al. (33), unlike U1a and U2 RNA, is associated with nuclear and cytoplasmic poly(A)-containing RNAs, this molecule may not only be involved in the splicing of hnRNAs, but also in transportation of mature mRNAs from the nucleus to the cytoplasm.

We are now examining the exact binding site(s) of the 4.5S

3' noncoding region



intron

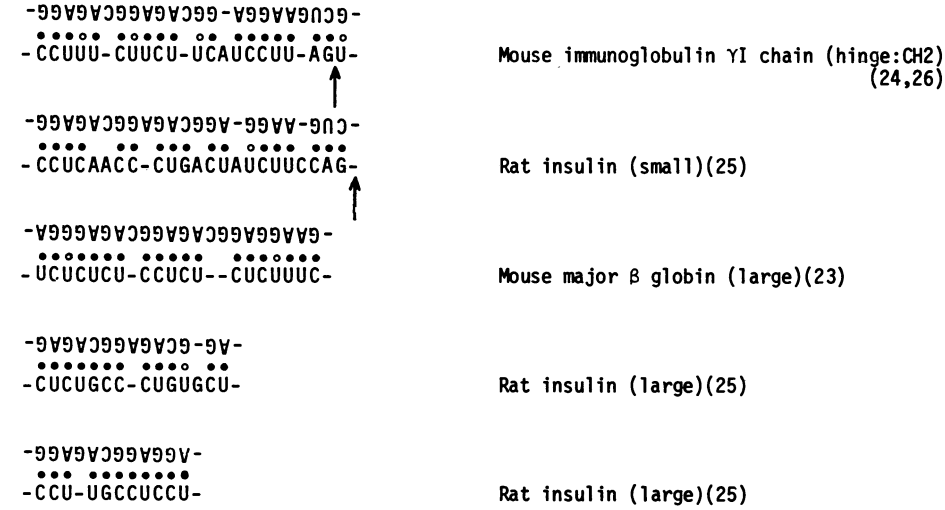


Figure 4. Possible hybrid structures between the purine-rich sequence of the 4.5S RNA (upper sequences) and pyrimidine-rich sequences of the 3'-noncoding regions and introns of rodent mRNAs or their precursors (lower sequences). Arrows indicate splice positions.

Table III. Comparison of sequences of the second protected site of the 4.5S RNA and splice junctions of rodent mRNA precursors

4.5S RNA	-GGCCAGC CUGGGCU-	-GGCCAGC CUGGGCU-
Mouse immunoglobulin		
λI chain (27)(leader:VL)	AGCUCAG GUCAGCA	UUUGCAG GGGCCAU
(VL:CL)	GUCCUAG GUGAGUC	UCCUGCG GCCAGCC
λII chain (27)(small)	UGCUCAG GUCAGCA	UUUGCAG GAGCCAG
γI chain (24,26)(CH1:hinge)	AAAAUUG GUGAGAG	UCCACAG UGCCCAG
(hinge:CH2)	UGUACAG GUAAGUC	UCCUUAG UCCCAGA
(CH2:CH3)	ACCAAAG GUGAGAG	CCCAGAG GCAGACC
γII b chain (28,29)(CH1:hinge)	AAACUUG GUGAGAG	UCUGCAG AGCCCAG
(hinge:CH2)	UGCCCAG GUAAGUC	UCAUCAG CUCCUAA
(CH2:CH3)	AUUAAAG GUGGGAC	CCCACAG GGCUAGU
Mouse major or minor β globin (23,30)		
(small)	UGGGCAG GUUGGUA	UUUUUAG GCUGCUG
(large)	CUUCAGG GUGAGUC	CCCACAG CUCCUGG (A)
Mouse α globin (31) (small)	UGGAAAG GUGAGAA	CUCCCAG GAUGUUU
(large)	CUUCAAG GUAUGCG	UCCGCAG CUCCUGA
Rat insulin (25) (small)	CAAGCAG GUAUGUA	CUUCCAG GUCAUUG
(large)	CCACAAG GUAAGCU	CUGGCAG UGGCACA
	5' junction	3' junction

Underlined bases of junctions were able to make hydrogen bonds with the sequence of the 4.5S RNA.

RNA to purified mRNA and viral RNA.

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NOTE After this manuscript was prepared, Lerner et al. reported a model that the 5'-terminal sequences of Ula RNA interact with the terminal sequences of the intervening regions (34). The 4.5S RNA has a similar sequence (residues 29 to 43) to the 5'-terminal sequence of Ula RNA. This sequence is also able to interact with the terminal sequences of the intervening regions.

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