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COMMENTARY

The signal recognition particle and related small cytoplasmic ribonucleoprotein particles

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SUMMARY

Recently, a number of novel small cytoplasmic ribonucleoprotein particles have been identified that comprise RNA and protein subunits related to the signal recognition particle (SRP). Here we discuss the latest results on the structure and functions of SRP together with the structures and putative functions of the novel SRP-related ribonucleoprotein particles.

Key words: Translocation, ER, Alu RNPs, 7SL RNA, Translational elongation

INTRODUCTION

Since the discovery of ribosomes, the number of RNA-protein complexes that play an important role in essential cellular functions has been growing tremendously. Particular progress was made in the identification and characterization of the structures and the functions of small ribonucleoprotein particles (RNPs) that localize to the nucleus. These snRNPs (small nuclear RNPs) or snoRNPs (small nucleolar RNPs) usually play a role in processes associated with RNA and DNA metabolism and the molecular mechanism of their action often implies base pairing of the RNA moiety with other nucleic acids.

In contrast, the number of small cytoplasmic RNPs (scRNPs) has remained less plentiful maybe because processes that imply interactions between nucleic acids are less numerous in the cytoplasm. Such processes could be related to translation, RNA turn-over and nuclear-cytoplasmic transport. The signal recognition particle (SRP), the most abundant and best characterized scRNP, functions in an intimate relationship with the ribosome to fulfill its essential role in the translocation of proteins into the endoplasmic reticulum (ER). Ro RNPs represent a group of scRNPs that share two protein subunits and contain RNA moieties of variable sizes but with a common secondary structure element. They are less abundant than SRP and their functions remain to be revealed (for review see van Venrooij et al., 1993).

Recently, several rare scRNPs have been discovered in mammalian cells that are composed of RNA and protein subunits related to SRP. The RNA moieties of the novel scRNPs are representatives of the Alu family of repetitive sequences in the primate and rodent genomes. In this commentary, we will briefly update our knowledge on the structure and functions of SRP and discuss the phylogenetic origins of SRP RNA-related scRNAs, as well as the structures and putative functions of these novel Alu scRNPs.

SRP DIRECTS NASCENT CHAINS OF PRESECRETORY PROTEINS TO THE TRANSLOCATION SITE IN THE ER IN A GTP-CONTROLLED FASHION

The first step in the secretory pathway of proteins is their translocation into the ER. A common hallmark of these proteins is a signal sequence that is usually located at their N-terminus and designates the proteins for ER-targeting. The functions of mammalian SRP in the translocation process are summarized in a model referred to as the SRP cycle (Fig. 1; for review see Walter and Johnson, 1994; Lütcke, 1995). In this model, SRP recognizes and binds specifically to the signal sequence of a nascent polypeptide thereby causing a pause in the elongation of the nascent chain. Targeting of the nascent chain to the translocation machinery is achieved by the guanine nucleotide-controlled interaction of SRP with the heterodimeric SRP receptor (SR) in the ER membrane. Upon release of the SRP-SR complex from the ribosome, protein synthesis resumes at its normal speed and, after a second signal sequence recognition event (Jungnickel and Rapoport, 1995; Belin et al., 1996), co-translational translocation of the nascent chain across or into the ER membrane takes place. SRP recycles by dissociating from its receptor in a process that requires GTP hydrolysis.

Mammalian SRP, purified from canine pancreas, contains one RNA molecule of 300 nucleotides (7SL or SRP RNA) and six polypeptides (Fig. 2). The signal sequences of nascent chains are bound by SRP54, a subunit of the S-domain of SRP. The primary sequence of SRP54 revealed a N-terminal GTP-binding domain (G-domain) and a methionine-rich C-terminal domain (M-domain). The M-domain contains the signal recognition and RNA-binding functions of SRP54 (Walter and Johnson, 1994; Lütcke, 1995, and references therein). Free SRP54 and SRP54 assembled into SRP both have the ability

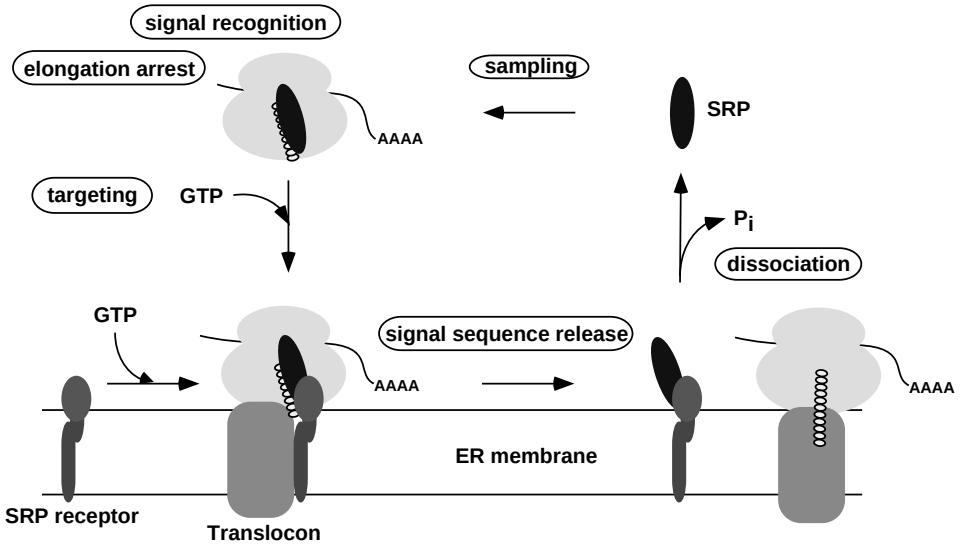


Fig. 1. SRP cycle. A model that describes the functions of SRP in the targeting of secretory proteins to the ER. The different symbols are labeled in the model. SRP54 and the α subunit of the SRP receptor have to be in the GTP-bound form to interact functionally. For a review on the translocon components see Schatz and Dobberstein, 1996, and references therein.

to bind specifically to signal sequences of nascent chains without additional cytosolic factors (Hauser et al., 1995; Powers and Walter, 1996). An important role for ribosomes in signal sequence binding by SRP54 was suggested by the finding that SRP does not bind to signal sequences of nascent chains that have been released from the ribosomes (Wiedmann et al., 1987; Garcia and Walter, 1988). Despite a common hydrophobic character, signal sequences have a very heterogeneous primary structure, and it therefore remains a challenging goal to determine how the specificity of the interaction between the signal sequence and SRP54 is achieved. It has been proposed that the clustered methionine residues with their flexible side chains in the M-domain may constitute the binding pocket for the hydrophobic signal sequence (Bernstein et al., 1989).

When bound to an evolutionary conserved structure in 7SL RNA (stem VIII in Fig. 2), SRP54 promotes targeting of the nascent chain by interacting with the heterodimeric SRP receptor (Miller et al., 1993; Hauser et al., 1995). Like SRP54, the two receptor subunits (SRα and SRβ) were found to contain GTP-binding domains (Lauffer et al., 1985; Miller et al., 1995). GTP-binding proteins have been found to regulate many biological processes by a mechanism which uses the interconversion between a GTP- and a GDP-bound form to modulate the interactions of GTP-binding proteins with other cellular components (Bourne et al., 1991). SRP54 and SRα have to be in the GTP-bound form to interact productively in the targeting process (Rapiejko and Gilmore, 1992; Bacher et al., 1996) and GTP hydrolysis is required for their dissociation (Connolly et al., 1991; Miller et al., 1993). Results obtained by studying the interactions between the homologues of SRP54 and SRα in *Escherichia coli*, ffh and ftsY, indicate that hydrolysis of GTP bound to SRP54 and to SRα occurs in a concerted fashion and is accomplished by the reciprocal stimulation of the GTPase activities of both proteins (Powers and Walter, 1995). GTP-binding to SRP54 was found to occur upon binding of SRP to the nascent chain-ribosome complex and is stimulated by a ribosomal component (Bacher et al., 1996). The requirements for GTP binding of the SRα as well as the role of GTP-binding of SRβ remain to be determined. The components of the minimal targeting machinery, SRP54, stem VIII of 7SL RNA and

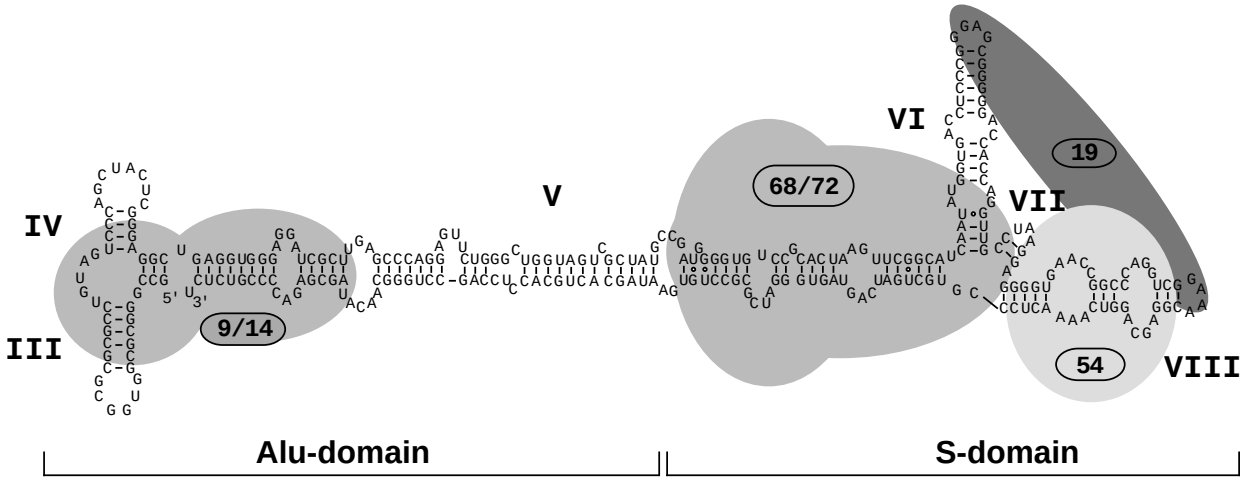


Fig. 2. Schematic representation of SRP. The protein subunits are named according to their relative molecular mass. The different stem structures of 7SL RNA are numbered according to the criteria of Larsen and Zwieb (1996).

SRα, are highly conserved in organisms of all three kingdoms and they have been shown to be involved in protein translocation in yeast and in *E. coli* (for review see Wolin, 1994; and for a compilation of the sequence data see the SRP database (Larsen and Zwieb, 1996)).

The role(s) of the other proteins in the S-domain of SRP is less well understood. SRP19 facilitates binding of SRP54 to 7SL RNA and the heterodimer SRP68/72 has been proposed to interact with SRα and its presence is required for binding of SRP to the ribosome (Siegel and Walter, 1988; Powers and Walter, 1996). In addition, SRP68/72 and the Alu-domain of SRP are required to confer elongation arrest activity to the particle. The finding that an SRP subparticle composed of SRP19, SRP54 and 7SL RNA promotes signal recognition and targeting of elongation-arrested chains (Hauser et al., 1995) but fails to promote co-translational translocation, suggests an important role for the elongation arrest function in adapting SRP to a co-translational mode of translocation.

THE ROLE OF SRP IN TRANSLATION

SRP has been found to be 20-fold less abundant than ribosomes in several mammalian cell lines (Bovia et al., 1995). To discern candidates for ER-targeting, SRP needs to interact directly and transiently with ribosomes, in a nascent chain-independent way.

Signal sequence-independent binding of SRP to polysomes had been detected in wheat germ extract (Walter et al., 1981). An extended study confirmed these results and demonstrated that the signal sequence-independent interaction of SRP with ribosomes is salt-sensitive and occurs exclusively with complete SRP (Powers and Walter, 1996). The molecular components that interact with each other are as yet unknown. SRP appears to be positioned correctly on the ribosome, even in the absence of a functional signal sequence, since SRP54 can be cross-linked to non-functional signal sequences and can be loaded with GTP, although both processes occur at lower efficiencies than in the presence of a signal sequence (Hauser et al., 1995; Bacher et al., 1996). Direct low affinity-binding of SRP to the ribosome may be modulated by other cellular components such as the nascent chain associated complex (NAC) (Wiedmann et al., 1994; Lauring et al., 1995; Powers and Walter, 1996).

A direct interaction between SRP and the ribosome was also indicated by the finding that SRP delays elongation of nascent chains that bear signal sequences. The elongation arrest activity of SRP is dependent on the signal recognition function and is observed as a complete arrest or as a kinetic delay in the elongation of secretory proteins depending on the in vitro translation system and on the preprotein used in the analysis. A molecular analysis of the effect of SRP on chain elongation revealed that ribosomes pause naturally at certain sites in mRNAs and that SRP enhances pausing of ribosomes at these specific sites (for review see Strub et al., 1993). The results of the in vitro experiments are consistent with a model (Rapoport et al., 1987) in which SRP exchanges rapidly between a ribosome-bound and free form. While bound to the ribosome, SRP completely arrests elongation whereas upon dissociation from ribosomes, protein synthesis resumes at its normal speed. The role of the elongation arrest function in protein translocation in vivo remains to be established. It is conceivable that it increases the efficiency of protein translocation by enlarging the time window during which the nascent chain can be targeted to the translocation site in a unfolded translocation-competent state.

In genetic experiments, SRP was found to interact with ribosomes at a specific step in the elongation cycle. The defect in growth and in protein translocation of yeast cells with limiting concentrations of SRP could be suppressed by slowing nascent chain elongation with a protein synthesis inhibitor, cycloheximide. Anisomycin failed to rescue the defective phenotype indicating that SRP interacts with ribosomes just before the peptidyl-tRNA undergoes translocation from the A to the P site (Brown, 1989; Ogg and Walter, 1995).

The components involved in elongation arrest activity of SRP are within the Alu-domain and include the 5′ and the 3′ ends of 7SL RNA and the heterodimeric protein SRP9/14 (Fig. 2). Particles which lack the entire Alu-domain of 7SL RNA or SRP9 and/or SRP14 are defective in the elongation arrest function (Siegel and Walter, 1986; Bovia et al., 1994). The defective phenotype of SRP lacking only one protein is explained by the finding that neither protein alone but only the heterodimer binds specifically to 7SL RNA (Strub and Walter, 1990). Whether the RNA or the protein moiety alone or both together interact directly with the ribosome to effect elongation arrest remains to be elucidated. The potential for base pairing between the loops of domains III and IV in 7SL RNA is highly conserved in evolution suggesting that they may fold into a structure that resembles tRNA (for a review see Zwieb, 1985). Such a tRNA-like structure could then interact directly with the ribosome to effect elongation arrest whereas SRP9/14 would act as a cofactor facilitating the process. A more direct role of the proteins has recently been suggested by the analysis of truncated SRP14 protein variants. A heterodimer composed of SRP9 and a truncated form of SRP14 competes efficiently with SRP9/14 for binding to 7SL RNA and concomitantly abolishes elongation arrest activity (Y. Thomas, N. Bui and K. Strub, unpublished).

The Alu-domain of 7SL RNA has been found conserved in eucaryotes and in archebacteria indicating that the translational control function of SRP is very ancient. In contrast to the stem VIII of 7SL RNA, it is, however, not present in all eubacteria (Larsen and Zwieb, 1996). One of the SRP9/14 binding regions, the mostly single stranded region between the two stem loop structures (see Fig. 4; Strub et al., 1991), was also found to be very conserved in its primary sequence throughout evolution suggesting the presence of SRP9/14 proteins in a large number of organisms. SRP14 has so far been identified in several mammalian species, in primates (Chang et al., 1994, 1995; Bovia et al., 1995), mouse and dog (Strub and Walter, 1989), in two plants (*Arabidopsis thaliana* and *Oryza sativa*; N. Bui, N. Wolff and K. Strub, unpublished results) and in yeast (Brown et al., 1994). The SRP14 proteins of higher primates (anthropoids) are considerably different from other SRP14 proteins in that they contain a C-terminal extension which is due to the amplification of a trinucleotide repeat in the coding region. The extension is mostly composed of alanines, few threonines and few prolines and ranges in size from 26 to 54 amino acids depending on the species (Chang et al., 1995). The additional domain has no effect on SRP9/14-binding to 7SL RNA and on the elongation arrest activity of

the particle (F. Bovia, N. Wolff, S. Ryser and K. Strub, unpublished).

WHAT IS THE ROLE OF 7SL RNA IN SRP FUNCTIONS?

The results outlined before suggest an important function for 7SL RNA as a scaffold for SRP assembly. The analysis of SRP RNA mutants in *Schizosaccharamyces pombe* further supports this view. A great number of single nucleotide changes were phenotypically silent indicating that the structure of SRP RNA is rather robust and that the overall structure may be functionally more important than single nucleotides. Conditional or lethal mutants had the mutations clustered in putative protein binding sites and their phenotype is therefore most likely explained by the accumulation of defective SRP particles and/or by a defect in SRP assembly (Liao et al., 1992).

Another possibility is that 7SL RNA could play a role in binding of SRP to other cellular components in the SRP cycle such as SR and ribosomes. The interaction with the ribosomes could be mediated by basepairing between rRNA and 7SL RNA and/or by binding of 7SL RNA to ribosomal proteins. Experimental evidence in support of this hypothesis is so far lacking. Conformational changes in the structure of 7SL RNA were observed between different SRP complexes isolated from canine pancreas, such as SRP alone, polysome-bound SRP and membrane-bound SRP (Andreazzoli and Gerbi, 1991). Thus, conformational changes in 7SL RNA may play a role in the cross-talk of different SRP domains and/or may regulate interactions with different cellular components. Sequential changes in 7SL RNA conformation may then help to move SRP through its cycle.

As mentioned before, a very attractive hypothesis, which remains to be tested, is the possibility that a tRNA-like structure in the Alu-domain of 7SL RNA may interact directly with the ribosome to effect elongation arrest.

THE 7SL RNA GENE AS A COMMON ANCESTOR FOR SEVERAL SMALL CYTOPLASMIC RNAs

Sequences related to 7SL RNA gene are abundantly dispersed throughout the mammalian genome and originate from the reverse flow of genetic information from 7SL RNA back into genomic DNA (Weiner et al., 1986). Amplification of the sequences at the 5′ and 3′ end of 7SL RNA gave rise to the Alu family of repetitive sequences which is specific for rodent and primate genomes. The Alu family of repetitive sequences is one of the most successful mobile genetic elements, having multiplied to 600,000 copies within the human genome in approximately 65 million years of primate evolution.

Recently, several Alu RNA species were found to accumulate stably in the cytoplasm of rodent and primate cells. The novel scRNPs comprising these RNAs are much less well characterized than SRP and nothing is known about their functions. The following chapters will therefore focus on the description of their structure and on the phylogenetic relationship between the RNA subunits as well as on the discussion of putative functions.

The oldest Alu-like sequences, fossil Alu monomers (FAMs), comprise one copy of the 97 and 60 base pairs at the 5′ and 3′ ends of the 7SL RNA gene, respectively (Fig. 3). FAM sequences diverged into two families: the families of the free left (FLAM) and the free right (FRAM) Alu monomers and the fusion between a member of each family is thought to be at the origin of the modern dimeric Alu family (Quentin, 1992a,b). The left and the right monomers lack internal sequences, as compared to the 7SL RNA gene, are connected by an A-rich linker and end in an oligo-A stretch (Figs 3, 4). Dimeric Alu sequences could be classified into subfamilies of different evolutionary age (Kapitonov and Jurka, 1996) and some members have been found to be actively retrotransposed until very recently (Batzer et al., 1996).

The Alu RNAs identified in the cytoplasm of primate cells include dimeric transcripts (Alu RNAs), processed small cyto-

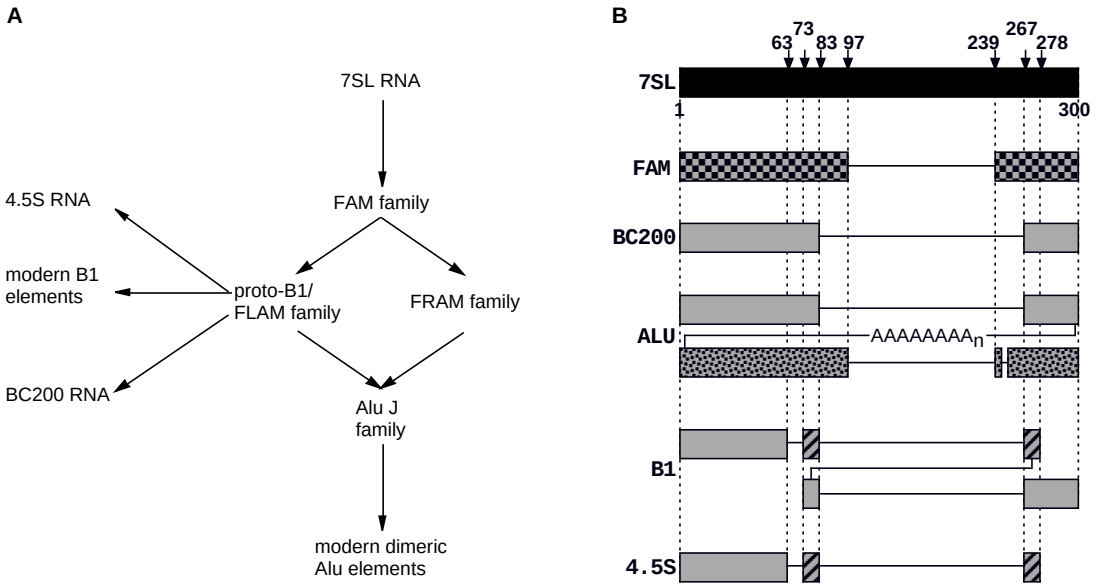
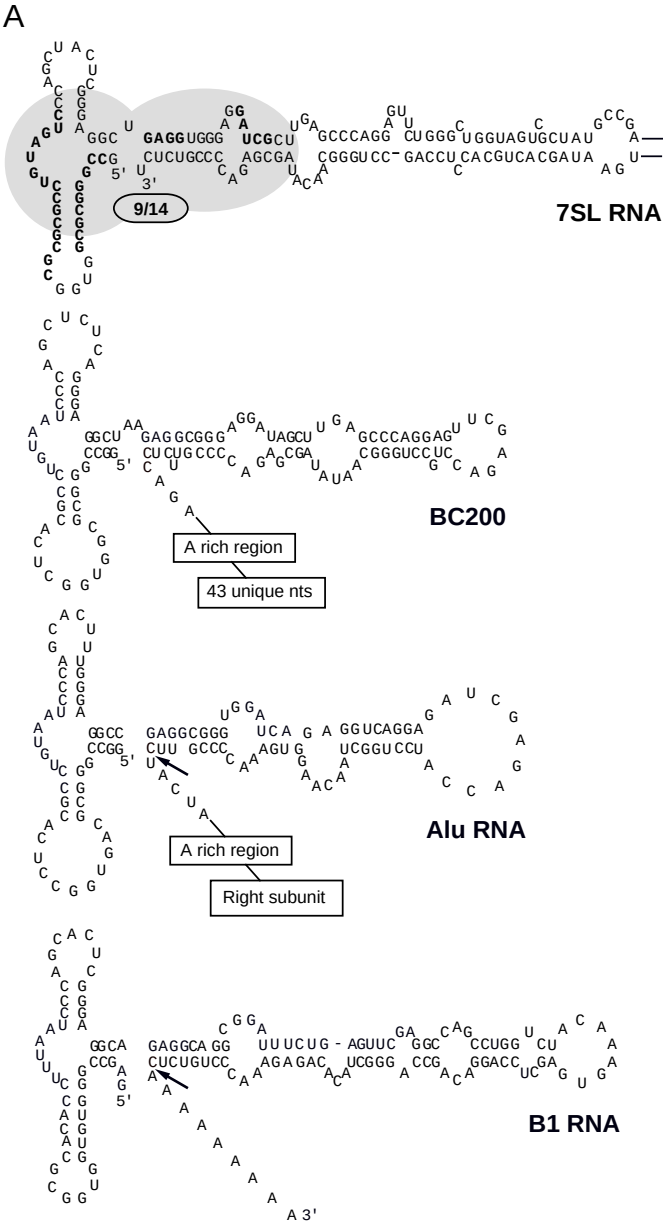


Fig. 3. (A) Evolutionary relationship between Alu-like elements. The FAM sequence family is closely related to the 7SL RNA gene and represents the oldest precursor of modern Alu-like elements identified so far. The 4.5 S RNA and BC200 RNA genes are closely related to the proto-B1/FLAM family and are therefore older than the modern B1 and Alu dimeric elements. (B) Architecture of Alu-like elements. A schematic representation of the Alu-portion of different genes derived from the terminal sequences of the 7SL RNA gene. This representation was adapted from that of Labuda and Zicetkiewicz (1994). Black squared and dotted areas stand for the FAM element and the Alu right monomer, respectively, and slashed areas represent the duplicated sequences in the B1 and the 4.5 S RNA genes.

A



B

RNA name	size	Abundance	Cruciform structure	SRP9/14 binding	RNP	S value
scAlu RNA	120 nts	10^3-10^4	+	+	+	8.5S
Dimeric Alu RNA	300-500 nts	10^2-10^3	+	+	+	11S
scB1 RNA	140 nts	10^3-10^4	+	+	+	?
BC200 RNA	200 nts	?	+	+	+	11.4S
4.5S RNA	95 nts	1.3 X 10^4	-	-	+	?

Fig. 4. (A) Structural comparison of the Alu portion of 7SL and related RNAs. Bold letters highlight the 4 contacts sites of SRP9/14 with 7SL RNA and the black arrows indicate the 3′ ends of scAlu and scB1 RNAs. (B) Abundance and composition of Alu-related RNPs. SRP9/14 binding to all RNAs was demonstrated in vitro. Furthermore, scAlu RNA was shown to be associated with SRP9/14 in vivo.

plasmic Alu RNAs (scAlu RNA) and BC200 RNA (Fig. 4). The primary sequences of scAlu and Alu RNAs indicate that they are transcribed from several genes representing predominantly younger Alu subfamilies (Maraia et al., 1993; Liu et al., 1994). The expression of scAlu RNAs is ubiquitous and rather stable whereas expression of dimeric Alu RNAs appears to be regulated by physiological factors, like cell stress (Chang and Maraia, 1993; Liu et al., 1995). BC200 RNA is specifically expressed in nerve cells from a single gene by polymerase III. Thus, it represents one of the few polymerase III genes that is expressed in a tissue specific manner. BC200 RNA has been detected in a subset of neurons where it localizes specifically to somatic and/or dentritic domains. The BC200 RNA gene is more closely related to the 7SL RNA gene than dimeric Alu sequences and contains, in addition to the Alu-like sequences at its 5′ end, a central adenosine-rich region and 43 unique terminal nucleotides (Watson and Sutcliffe, 1987; Martignetti and Brosius, 1993a; Tiedge et al., 1993).

The rodent genomes contain a proto-B1 element with high homology to the FLAM elements of primates, suggesting that both are lineage-specific names for the same family of primitive Alu/B1 elements (Fig. 3). In contrast to the Alu elements, the B1 elements remained monomeric during evolution and contain an internal tandem repeat of 29 bp and a deletion of 9 bp (Fig. 3; Quentin, 1994). A subset of B1 elements is expressed as processed small cytoplasmic B1 RNAs (scB1) (Adeniyi-Jones and Zasloff, 1985; Maraia, 1991). The 4.5 S RNA genes represent another B1 family (Fig. 3). They are abundant in the mouse and rat genomes (850 and 690 copies per haploid genome, respectively) and are organized in tandemly repeated arrays, most likely at a single locus (Schoeniger and Jelinek, 1986). The 4.5 S RNA genes lack internal and 3′ terminal sequences as compared to 7SL RNA (Fig. 3; Jelinek and Schmid, 1982).

STRUCTURE OF ALU-RELATED scRNPs

The rodent scB1 and the primate scAlu RNAs accumulate to approximately 10^3-10^4 copies per cell which is about 50- to 100-fold less abundant than SRP RNA (Chang and Maraia, 1993; Fig. 4). The scB1 and scAlu RNAs comprise 135 and 120 nucleotides, respectively, and are generated from the primary transcripts by an endonucleolytic cleavage that removes the poly(A) tract in the monomeric B1 transcript and the poly(A) tract and the right Alu arm in the dimeric Alu transcript (Fig. 4; Adeniyi-Jones and Zasloff, 1985; Maraia et al., 1993). As mentioned before, their primary sequences diverge, however, their secondary structures remained more highly conserved as predicted from random Alu sequences (Maraia et al., 1993). The best conserved domains are stems III, IV, and the first part of stem V as well as nucleotides 23 to 47 (Figs 2, 4; Labuda and Zicetkiewicz, 1994; Kariya et al., 1987). These regions include all four contact sites of SRP9/14 with 7SL RNA (Fig. 4; Strub et al., 1991) and scAlu and scB1 RNAs were indeed found to bind to the heterodimeric SRP subunit, SRP9/14, in vitro (Chang and Maraia, 1993; Chang et al., 1994; Bovia et al., 1995,). Furthermore, scAlu RNA was shown to exist as an 8.5 S particle together with SRP9/14 in HeLa cells (Bovia et al., 1995). The similarity in structure and abundance of scAlu and scB1 RNAs, together with their ability

to bind SRP9/14, indicates that primate scAlu and rodent scB1 RNAs represent functional homologues.

Dimeric Alu RNAs of 300 to 500 nucleotides are tenfold less abundant than scAlu RNAs and exist as cytoplasmic 11 S particles in vivo (Liu et al., 1994). BC200 RNA exists as an 11.4 S particle in neuronal brain tissue (Jr-G. Cheng, H. Tiedge and J. Brosius, personal communication). Both BC200 and Alu RNAs bind to SRP9/14 in vitro and the stability of the RNA-protein complex decreases in parallel with their phylogenetic relatedness to 7SL RNA (F. Bovia, N. Wolff, S. Ryser and K. Strub, unpublished; D. Zopf and J. Brosius, personal communications). The results of the in vitro RNA-binding experiments together with the observation that free SRP9/14 exists in a 20-fold excess over SRP in anthropoid cells (Bovia et al., 1995; Chang et al., 1995) indicates very strongly that all cytoplasmic Alu-like RNAs are associated with the heterodimer in vivo.

The abundance of 4.5 S RNA is similar to one of the scAlu RNAs (Schoeniger and Jelinek, 1986) and its primary sequence is well conserved in all rodent species (Jelinek and Schmid, 1982). However, the typical cruciform structure at the 5′ end of 7SL RNA has not been conserved in 4.5 S RNA (Labuda and Zicetkiewicz, 1994) and 4.5 S RNA does not bind to SRP9/14 (F. Bovia, N. Wolff, S. Ryser and K. Strub, unpublished). The RNA exists as an RNP which is specifically recognized by anti-La autoantibodies. The La protein is known to bind to the poly U stretch of newly synthesized polymerase III transcripts. The 4.5 S RNA is cytoplasmic and nuclear and has a short half-life in both compartments (Jelinek and Leinwand, 1978; Leinwand et al., 1982). It has the capacity to form base-paired duplexes with poly(A)-containing hnRNAs and mRNAs. However, it dissociates from the mRNAs upon formation of polysomal complexes (Jelinek and Leinwand, 1978; Schoeniger and Jelinek, 1986). Cytoplasmic accumulation and nuclear export of 4.5 S RNA is linked to mRNA metabolism. The 4.5 S RNA is not exported into the cytoplasm when the transport of poly(A) RNA is inhibited and 4.5 S RNA accumulation in the cytoplasm ceases concommittantly with a change in the mRNA population during differentiation of cultured rat myoblasts (Leinwand et al., 1982).

From the results outlined above, 4.5 S RNP is clearly distinct from the other Alu scRNPs. The RNA lost the specific cruciform structure and is not bound to SRP9/14. Its localization and its association with poly(A) RNAs suggest that the 4.5 S RNP may be involved in shuttling of mRNA between nucleus and cytoplasm. Notably, it is the only scRNP for which the RNA moiety has been shown to interact with other nucleic acids.

DO ALU RNPs HAVE A ROLE IN TRANSLATION?

The stable accummulation of matured Alu and B1 RNAs in many different cell types and the regulated expression of BC200 RNA together with their association with SRP9/14 suggest a cellular function for these scRNPs. We favor the hypothesis that Alu scRNPs have a function in translation. This hypothesis is supported by the striking structural similarity between Alu scRNPs and the Alu-domain of SRP. Whether Alu scRNPs can bind to ribosomes remains to be examined. It is, however, indicated by the findings that signal-sequence independent binding of SRP to ribosomes relies on elements within the Alu-domain of SRP (Hauser et al., 1995; Powers and Walter, 1996). Alu RNPs are a thousandfold less abundant than ribosomes and may therefore interact with only a selected pool of ribosomes. As compared to SRP, they lack the signal recognition function and the specificity of their effect on translation would have to be achieved by other means. Possibly, it could be provided by other protein subunits of the particles. The existence of such additional proteins is suggested by the sedimentation coefficient of scAlu RNP. Alternatively, the specific intracellular location of the particles may guarantee specificity. The latter hypothesis is supported by the specific somatodendritic location of BC200 RNAs. Interestingly, a putative functional homologue of BC200 RNA in rodent cells, the small cytoplasmic BC1 RNA, is phylogenetically related to $tRNA^{Ala}$. BC1 RNA has the same specific expression pattern and the same subcellular location as BC200 RNA. In addition, it shares sequence similarity with BC200 in the central A-rich and the 3′ unique sequences (Watson and Sutcliffe, 1987; Tiedge et al., 1993; Martignetti and Brosius, 1993b). BC1 RNA also exists as an RNP (Kobayashi et al., 1991) but does not bind to SRP9/14 in vitro (F. Bovia, N. Wolff, S. Ryser and K. Strub, unpublished). Thus, both RNAs may have been independently recruited to accomplish neuron-specific functions in primates and rodents, respectively. A function for these RNPs in association with the ribosome is indicated by the observation that both RNAs have ancestral progenitors, tRNA and 7SL RNA, that are intimately involved in the translational processes. Further biochemical characterization of the novel scAlu RNPs together with the unravelling of the mechanism of the elongation arrest function of SRP may allow us to identify putative Alu RNP functions in the future.

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