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Review

Small nucleolar RNAs

G. L. Eliceiri

Department of Pathology, Saint Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis (Missouri 63104-1028, USA), Fax + 1 314 577 8489, e-mail: eliceiri@slu.edu

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Abstract. Many small RNA species associate with the nucleolar structure. Some of these small nucleolar RNAs (snoRNAs) are required for cleavage processing of ribosomal RNA precursors. There are many pseudouridine residues and methylated riboses in mature ribosomal RNA. For most, if not all, of these modifications, each site is selected by base pairing with a specific snoRNA species. Some snoRNAs are needed for the 2′-O-ribose methylation of at least one spliceosomal small nuclear RNA. Many snoRNAs, particularly in yeast, are generated from independent transcription units. Most vertebrate snoRNAs are produced by processing of introns from protein-coding transcripts. Some snoRNAs are made by processing of introns from non-protein-coding transcripts.

Key words. Small nucleolar RNAs; ribosomal RNA precursor cleavage; 2′-O-ribose methylation; pseudouridine formation; intron-encoded RNAs.

Introduction

The nucleolus is a dynamic nuclear structure that reassembles after each mitosis. It is the site of transcription and processing of ribosomal RNA (rRNA) and assembly of each ribosomal subunit [1, 2]. Many small nucleolar RNAs (snoRNAs) have been identified. Their association with the nucleolus has been determined by subcellular fractionation and cell microscopy, or has been inferred from their association with an rRNA precursor (pre-rRNA) or known nucleolar proteins, or the presence of known snoRNA-sequence motifs in their sequences. The study of snoRNAs has revealed many surprises recently, such as the very large number of different snoRNA species per cell, their wide variety of functions, their various RNA substrates and their different biosynthetic pathways. This review focuses on recent advances in our knowledge of snoRNAs, primarily in progress made since the last overall reviews of this subject [3–6].

Conserved sequence elements and secondary structures of snoRNAs

It is anticipated that there may be about 200 different snoRNA species per vertebrate cell [7]. Most snoRNAs have been identified in either yeast or vertebrates; a few have been identified in both (tables 1 and 2). Their sizes range between ~ 67 and 608 nucleotides [3, 8]. The number of molecules of a snoRNA species per cell ranges in vertebrates between $\sim 2 \times 10^5$ for U3 RNA and $\sim 1–2 \times 10^4$ to 10^3 for other snoRNAs, and between $\sim 10^2$ and 10^3 in yeast [3, 9, 10].

SnoRNAs can be divided into three families, based on their conserved sequences and structures. Box C/D snoRNAS have the conserved sequence elements named box C (UGAUGA) and box D (CUGA) near the 5′ and 3′ ends, respectively, and usually have a base-paired 5′, 3′ terminal stem [3, 9] (fig. 1A). Most C/D snoRNAs have an additional, internal copy of these boxes, C′ and D′, that normally contain one or two base substitutions [11]. Boxes C and D are needed for metabolic stability

of the mature snoRNA [12–14]. In the second family, box H/ACA snoRNAs have the motif ACA (which almost always has a C residue in the second position) located three nucleotides from their 3 ends, can fold into a 'hairpin-hinge-hairpin-tail' secondary structure and have the sequence ANANNA (box H) in the hinge region [15, 16] (fig. 1B). The third class consists of nuclear RNase MRP and RNase P, ribonucleoprotein enzymes that share substantial sequence and secondary structure [17–22]. The nucleotide modifications of almost all snoRNA species are unknown.

Ribonucleoprotein particles of snoRNAs

SnoRNAs are present in small nucleolar ribonucleoprotein particles (snoRNPs) in vivo. There has been substantial progress in our knowledge of yeast snoRNP proteins. Fibrillarin, a nucleolar protein (Nop1p is its yeast ortholog), associates with all box C/D snoRNA species; boxes C and D are required for this binding [3]. Nucleolar proteins Sof1p and Mpp10p are apparently specific for one C/D snoRNA, U3 [3, 23, 24]. All yeast H/ACA snoRNAs that have been tested associate with the nucleolar proteins Gar1p, Cbf5p, Nhp2p and Nop10p [25–28]. A putative nucleic acid helicase, Sen1p, associates both with C/D and H/ACA snoRNAs [29]. Yeast protein Snm1p is specific for RNase MRP. All the yeast proteins just mentioned, plus yeast snoRNA-associated proteins Nop5p and Nop56p, are involved in pre-rRNA processing, but their precise functions are unknown [3, 23, 24, 26–31]. Only two H/ACA snoRNA species are known to be associated with the nucleolar protein Ssb1p [32]. Most of the snoRNP proteins remain to be identified. Yeast nuclear RNase P is a ribonucleoprotein consisting of one RNA and nine proteins; one of these proteins is unique to RNase P, and the other eight are apparently shared with RNase MRP [33].

Genes and biosynthesis of snoRNAs

The biosynthesis of snoRNAs follows different pathways. Most of the yeast snoRNAs and a few of the vertebrate snoRNAs are transcribed from independent transcription units [3]. Most of these are apparently transcribed by RNA polymerase II, thus containing a 5′-end trimethylguanosine cap, such as U3 snoRNA from organisms other than plants, U8 and U13 snoRNAs [3]. A few are transcribed by RNA polymerase III, resulting in a 5′-terminal triphosphate, such as RNase MRP RNA in multicellular organisms, or a 5′-end γ-monomethyl phosphate cap, such as plant U3 snoRNA [3, 5]. Most plant snoRNAs and many yeast snoRNAs are processed from polycistronic snoRNA precursors [3, 8].

Most vertebrate snoRNAs are encoded in introns of protein genes [3, 34–40]. The majority of the snoRNA host genes encode proteins needed for ribosome biosynthesis or function, such as ribosomal or nucleolar proteins or protein synthesis factors [3]. Some snoRNAs are generated from introns of non-protein-coding genes [41–44]. Transcription starts with a C residue followed by a polypyrimidine tract in genes of the 5′-terminal oligopyrimidine (5′TOP) family. Both the non-protein-coding and the protein-coding snoRNA host genes have features of the 5′TOP genes [41, 43, 44]. The 5′ ends of intron-encoded snoRNAs are not capped, but contain an unmodified monophosphate [3].

There are 45 C/D and 20 H/ACA known snoRNAs in *Saccharomyces cerevisiae*. Among the yeast C/D snoRNAs, 22 are monocistronic, 17 are polycistronic and 6 (U18, U24, snR38, snR39, snR54 and snR59) are

Table 1. Vertebrate small nucleolar RNAs.

snoRNA	Box elements	Function	References
U3	C/D	C	72, 73
U8	C/D	C	12, 76
U22	C/D	C	75
U14	C/D	C; M	71, 108
U25	C/D	M	107
U15, U16, U18, U20, U21, U24, U26–U63, U73–U81	C/D	M*	111–114
mgU6–47	C/D	MU6*	118
mgU6–77	C/D	MU6	118
E1/U17	H/ACA	C	71, 79
E2	H/ACA	C; ψ*	79, 179
E3	H/ACA	C; ψ*	71, 79, 179
U19, U23, U64–U72	H/ACA	ψ*	179
Rnase MRP	–	–	128

C, pre-rRNA cleavage; M, pre-rRNA 2′-O-methylation; ψ, pre-rRNA pseudouridylation; MU6, 2′-O-methylation of U6 snRNA.
*Predicted by motif analysis.

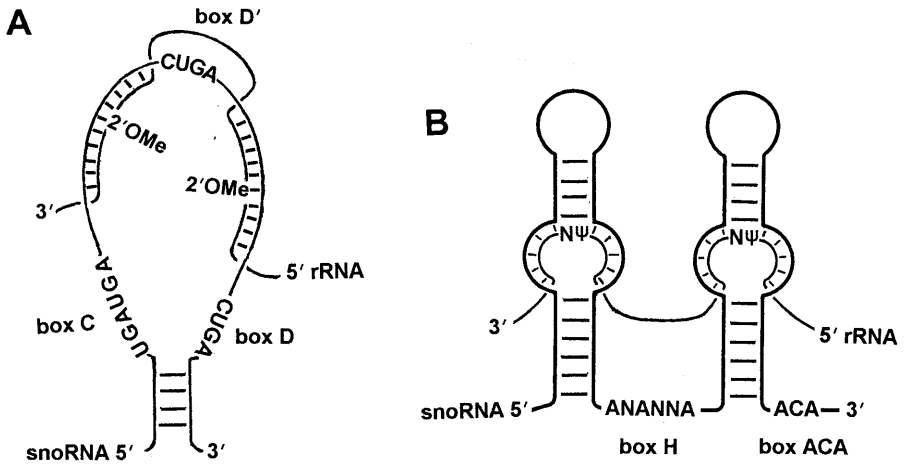

Figure 1. Models of snoRNA structures and of base-pairing interactions between pre-rRNA and snoRNAs that direct site-specific modifications. (*A*) Box C/D snoRNA guiding pre-r-RNA 2′-O-ribose methylation [7, 47, 107]. (*B*) Box H/ACA snoRNA directing pre-RNA pseudouridylation [121].

intronic [8, 45, 46]. One of the yeast H/ACA snoRNAs is intronic (snR44), and the others are monocistronic [8]. There are 50 C/D and 14 H/ACA known vertebrate snoRNAs. Three of these C/D snoRNAs are encoded in independent genes; these H/ACA snoRNAs and the rest of the C/D snoRNAs are intronic [3, 41, 47]. The gene organization of a snoRNA may differ in various organisms. For example, U14 RNA genes are intronic in vertebrates, independent in yeast and tandemly arranged in maize [3]. The main E1/U17 snoRNA species of human (HeLa) cells has an extra nucleotide (U) at position 19 that its intronic gene lacks, that is compatible with the possibility of some form of RNA editing [39].

Most of the intronic snoRNAs are processed exonucleolytically from excised introns [48–51]. Processing of some vertebrate intronic snoRNAs is apparently independent of pre-messenger RNA (mRNA) splicing [49, 50]. Processing of yeast intronic snoRNAs depends on an RNA lariat-debranching enzyme (Dbr1p), supporting the conclusion that these snoRNAs are normally produced via a pre-mRNA splicing-dependent pathway [52, 53]. The available evidence supports the conclusion that two frog intronic snoRNAs, U16 and U18, are generated by endonucleolytic cleavages of the host pre-mRNAs, alternative to mRNA splicing, followed by exonucleolytic trimming [14, 54].

Elements sufficient for H/ACA and C/D snoRNA processing lie within the mature snoRNA sequence [48, 55]. C/D snoRNA processing requires boxes C and D; vertebrate U14 snoRNA processing and U14 RNA accumulation in yeast also require a base-paired 5′, 3′ terminal stem [55–57]. Hypermethylation of the 5′ cap requires box D in U3 and U8 snoRNAs and a 3′ base-paired stem in U3 RNA [13]. In H/ACA snoRNAs, boxes H and ACA are essential for snoRNA correct 5′ and 3′ end formation, respectively, and for snoRNA accumulation [15, 16, 58].

The proteins required for snoRNA processing are beginning to be identified. Yeast pre-rRNA and intronic and polycistronic snoRNAs require common molecules for processing [52]. A putative nucleic acid helicase, Sen1p, is required for processing and accumulation of yeast C/D snoRNAs [59]. Yeast snR190 and U14 snoRNAs are cotranscribed; Rnt1p, an endoribonuclease that is the yeast ortholog of RNase III, cleaves the dimeric precursor, and trimming by $5' \rightarrow 3'$ exonucleases Rat1p and Xrn1p generates the mature snoRNAs [4, 52, 60]. Seven yeast C/D snoRNAs (snR72–snR78) are processed from a common polycistronic precursor by Rnt1p and Rat1p [46]. Rnt1p depletion blocks the maturation of 20 C/D and H/ACA snoRNA species out of 46 snoRNAs tested; most of them are polycistronic, some are monocistronic, two are dicistronic and none is intron-encoded [61]. A non-fibrillarin trans-acting factor binds the C/D box terminal motif, is essential for C/D snoRNA processing and is common to intronic and nonintronic C/D snoRNAs [55, 62].

The maturation of box C/D snoRNAs occurs in the nucleoplasm [13, 57]. In contrast to 5′ trimethylguanosine-capped spliceosomal small nuclear RNAs (snRNAs), the U3, U8 and U14 snoRNA precursors are not exported to the cytoplasm during processing [13]. The 5′ 7-monomethylguanosine-capped U3

snoRNA precursor remains in the nucleus where it undergoes 5′ cap trimethylation [63].

Intracellular localization elements of snoRNAs

SnoRNAs require cis-acting elements for their nucleolar localization (i) right after their synthesis in the nucleoplasm, to be transported to the nucleolus, and (ii) as mature molecules, to return to the nucleolus after mitosis and remain there between mitoses. Boxes C and D are necessary for nucleolar localization of vertebrate and yeast C/D snoRNAs [57, 64–66]. There are apparently differences between the localization requirements in vertebrates and yeast. The C/D box terminal stem is needed for snoRNA nucleolar localization in yeast [57], but not in vertebrates [64, 66]. There are differences between the requirements of various C/D snoRNA species. First, box D is necessary for the nuclear retention of vertebrate U8 RNA, but not U3 RNA [13]. Second, the spatial position of boxes C and D is essential for nucleolar localization of vertebrate U14 snoRNA, but not U8 snoRNA [64, 65]. The single-stranded segment immediately 5′ of box C is needed for U8 RNA nucleolar localization [65]. The hinge region, box B and box C′ of vertebrate U3 RNA affect the efficiency of its nucleolar localization [66]. There might be requirement differences between amphibian oocytes and mammalian, dividing somatic cells. When the 5′ end of U3 RNA is blocked with the abnormal cap (5′)Appp(5′)G, this snoRNA can still localize in nucleoli in frog oocytes [66], but not in rat kidney cells [67]. Other experiments suggest that this difference extends to U8 snoRNA [65, 67].

Nucleotides 23–62 of RNase MRP RNA, that include the binding site for the nucleolar protein *To*, are needed for the nucleolar localization of this RNA [68]. Shortly after RNase P is injected, it localizes in the nucleolus; nucleotides 1–88 of this RNA are necessary and sufficient for this localization [69].

Functions of snoRNAs in ribosome formation

Pre-rRNA cleavage

In principle, snoRNAs might have one or more of several possible functions in ribosome biogenesis, including folding of pre-rRNA as chaperones, direct roles in pre-rRNA cleavage, transport of pre-rRNAs or factors during maturation, presentation of RNases to pre-rRNA processing sites or assembly of ribosomal subunits. Cleavage processing of pre-rRNA requires some box C/D snoRNAs, some box H/ACA snoRNAs, and RNases MRP and P [12, 17, 18, 20, 70–79] (tables 1 and 2). Some snoRNA species are needed at more than one processing site; a given processing site requires more than one snoRNA species, these snoRNAs possibly functioning as a multi-snoRNP complex or 'processome' [17, 74, 80]. For example, U14 snoRNA is required for processing at the 5′ external transcribed spacer (5′ETS) and near both ends of the 18S rRNA sequence [70, 71]; U3 snoRNA is needed at the 5′ETS, near both ends of 18S rRNA, and the 5′ end of 5.8S rRNA [72–74]; U22 snoRNA at both ends of 18S rRNA [75]; and U8 snoRNA at both ends of the 5.8S rRNA and of the 28S rRNA sequences [12, 76]. Progress in the study of the functions of these snoRNAs has been hindered by the lack of snoRNA-dependent pre-rRNA processing in vitro systems. There is no eukaryotic cell-free system now that returns to normal pre-rRNA cleavage processing upon addition of an in vitro-synthesized snoRNA to an extract that had been depleted of that snoRNA [71].

Table 2. Yeast small nucleolar RNAs.

snoRNA	Box elements	Function	Essential	References
U3	C/D	C	+	74
U14	C/D	C; M	+	47, 70
U8, U24, snR13, snR38-snR41, snR50–snR58, snR60–snR79	C/D	M	–	8, 45–47
snR39b, snR47, snR48	C/D	M	n.d.	8, 45
snR59, snR190	C/D	M*	–	45, 47
snR4, snR45	C/D	–	–	8
snR10	H/ACA	C; ψ	ts	77, 120
snR30	H/ACA	C	+	78
snR3, snR5, snR8, snR31-snR37, snR42, snR46	H/ACA	ψ	–	120, 121
snR11, snR44, snR189	H/ACA	ψ*	–	121
snR49	H/ACA	ψ*	n.d.	121
snR9, snR43	H/ACA	–	–	8
RNase MRP	–	C	+	17, 18
RNase P	–	C	+	22

n.d., not determined; ts, temperature-sensitive; other abbreviations as in table 1.

Several snoRNA elements needed for pre-rRNA cleavage have been identified. Boxes B and C and the 5′ portion of yeast U3 snoRNA are needed for its function in pre-rRNA processing [81]. The following yeast U3 snoRNA domains are essential for pre-rRNA processing: (i) domain A, a conserved sequence that base-pairs with an 18S rRNA sequence; and (ii) the Y domain, a stem-loop structure that resides between the two universal sequences that base-pair with 18S rRNA sequences, is conserved in yeasts and is absent in vertebrates [3, 82]. The sequence of the 5′ terminal 15 nucleotides of U8 snoRNA is needed for 5.8S and 28S rRNA processing, and shows complementarity to a segment of 28S rRNA that interacts with 5.8S rRNA in mature rRNA [83].

Several snoRNA:pre-rRNA interactions have been shown to be necessary for pre-rRNA cleavage processing. Compensatory mutation analysis has revealed interactions between U14 snoRNA and 18S rRNA sequences [84] and between U3 snoRNA and 5′ETS [85] that are required for 18S rRNA processing. A base-pairing interaction between yeast U3 snoRNA and 18S rRNA sequences, which is needed for pre-rRNA processing, suggests that U3 RNA may facilitate correct folding of a conserved pseudo-knot in 18S rRNA [86, 87]. Psoralen cross-linking has revealed contacts between the yeast 35S pre-rRNA primary transcript and three U14 snoRNA regions: (i) the Y domain, a stem-loop structure that is required for pre-rRNA processing [82]); (ii) domain A, which is complementary to an 18S rRNA sequence; and (iii) the sequence between box C and domain A [88]. Cross-links between U14 snoRNA and other small RNA species have been shown in yeast [88]. There are several interactions between U3 sno RNA and 5′ETS, near and far, as well as 5′ and 3′, from the 5′ETS cleavage site [3, 87, 89, 90].

Two isolated RNases are known to cut pre-rRNA correctly. Purified RNase MRP accurately cleaves yeast pre-rRNA at processing site A_3, which is located upstream of the 5.8S rRNA sequence [91]. RNase III cuts yeast pre-rRNA in vitro at a site that is U3 sno RNP-dependent in vivo [92]. In addition, RNase P RNA is involved in pre-rRNA cleavage processing in yeast [22].

Many nucleolar proteins that are not known to be integral components of snoRNPs, are necessary for ribosome biogenesis in yeast. For example, nucleolin, Nsr1p, Nop77p, Dim1p, Nop4p and Rrp5p affect pre-rRNA processing [93–96]. Several putative RNA helicases, such as Rok1p, Dob1p, Dbp7p, Spb4p and Dbp4p, are required for pre-rRNA processing or ribosomal subunit formation in yeast [97–101]. Five essential exonucleases, in an 'exosome' complex, are needed for pre-rRNA processing in yeast [102, 103].

2′-O-Ribose methylation of preribosomal and other RNAs

There are approximately 100 2′-O-methylated riboses in vertebrate rRNA and about 55 in yeast rRNA, limited only to the most conserved regions of mature rRNA [104]. These modifications occur early, apparently during pre-rRNA transcription [104]. Most of the known C/D snoRNAs have 10–21-nucleotide sequences complementary to universal core regions of mature rRNA [105, 106]. SnoRNA depletion experiments have shown that many box C/D snoRNA species serve as sequence-specific guides for pre-rRNA 2′-O-methylation by direct base pairing of the snoRNA and rRNA [45, 47, 107, 108] (reviewed in [109–112]) (tables 1 and 2). Other C/D snoRNA species are expected to be needed for pre-rRNA ribose methylation, based on sequence complementarity between these snoRNAs and pre-rRNA 2′-O-methylation sites [113, 114]. The snoRNA elements needed for rRNA ribose methylation are either the downstream antisense element and terminal boxes C and D, or the upstream antisense element and internal boxes D′ and C′ [115–117] (fig. 1A). Boxes D and D′ apparently function as molecular measuring devices, since the fifth nucleotide upstream of these boxes determines the methylation site [115]. Correct spacing between boxes D′ and C′ is needed for efficient rRNA methylation [115]. A short fragment of a methylation guide snoRNA containing the complementary (antisense) element and boxes D′ and C′ is sufficient to guide rRNA 2′-O-methylation [115]. U3, U8 and U22 RNAs, C/D snoRNAs that are needed for pre-rRNA cleavage but apparently not for ribose methylation, lack an antisense element immediately upstream of box D [47, 115]. The molecule(s) that catalyzes the 2′-O-methylation of riboses in eukaryotic pre-rRNA is not known.

Some recently discovered snoRNAs are needed for the site-specific nucleotide modification of other small RNA species, that are nuclear but not nucleolar. Two C/D snoRNAs, mgU6-47 and mgU6-77, have the expected sequences to guide the 2′-O-methylation of U6 spliceosomal snRNA; mgU6-77 RNA is required for the ribose methylation of both U6 snRNA and 28S rRNA [118]. Mature U6 and U2 spliceosomal snRNAs are nucleoplasmic. When newly made, these snRNAs pass through the nucleolus (P. Ganot, M.-L. Bortolin and T. Kiss, personal communication).

Pre-rRNA pseudouridine formation

There are about 95 pseudouridine residues in vertebrate rRNA and 44 in yeast rRNA, only in the most conserved segments of mature rRNA [119]. It has been shown experimentally in yeast that many H/ACA snoRNA species function as site-specific pre-rRNA pseudouridylation guides via snoRNA:pre-rRNA base

pairing [120, 121] (reviewed in [7, 119]) (tables 1 and 2). Based on sequence complementarity between other pre-rRNA pseudouridylation sites and single-stranded sequences in internal loops of H/ACA snoRNAs, additional H/ACA snoRNA species are predicted to be necessary for pre-rRNA pseudouridine synthesis [121]. (Prokaryotic RNA pseudouridine synthases do not use guide RNAs to recognize pseudouridylation sites). Base pairing between the snoRNA and eukaryotic pre-rRNA is essential for pseudouridine formation [120, 121]. Pseudouridylation guide snoRNAs have an internal loop structure, named the 'pseudouridylation pocket', that has the potential to base-pair with rRNA forming two short (3–10 bp) helix structures separated by two unpaired rRNA nucleotides [121] (fig. 1B). Box ACA or H lie 14–16 nucleotides 3′ of the modification site in the pseudouridylation pocket [120, 121]. These boxes appear to be molecular measuring devices, since the distance from the ACA box determines the pseudouridylation site [120]. The H and ACA boxes, and the 5′ and 3′ hairpin domains, are all essential for rRNA pseudouridylation [58]. None of the snoRNAs only known to guide pre-rRNA pseudouridine formation or ribose methylation appear to be essential for pre-rRNA cleavage processing [3, 109].

Based on computer analysis, it has been proposed that all H/ACA snoRNAs have the same secondary structure and that most H/ACA snoRNAs guide pre-rRNA pseudouridine synthesis [119]. However, for some vertebrate H/ACA snoRNA species, these proposals should be tested experimentally. For example, the E1 and E3 snoRNA secondary structure models based on sequence phylogeny [122] are substantially different from the proposed single secondary structure of all rRNA pseudouridylation guide snoRNAs [121]. The H (ANANNA) box is present in, and proposed to be essential for, all the snoRNAs that direct pseudouridine formation [121], but this sequence is not phylogenetically conserved in E3 snoRNA [122]. The proposed role of E2 snoRNA in the pseudouridylation of residue 3731 of human 28S rRNA is based on (i) complementarity in 7 and 8 contiguous nucleotides flanking that site in human RNA, and (ii) the hypothesis that these two snoRNA sequences are single-stranded, in an internal loop [121]. However, many of these nucleotides are not evolutionarily conserved and have not covaried, leaving only four and three noncontiguous complementary residues, respectively, flanking that site, and these E2 RNA sequences are base-paired in the snoRNA secondary structure model developed from sequence phylogeny [122, 123]. The proposal that E3 RNA directs pre-rRNA pseudouridine synthesis is based on the hypothesis that two specific E3 RNA sequences are in an internal loop [121], but these sequences are in single-stranded stems in the E3 RNA secondary structure model obtained from sequence phylogeny [122]. There are no pseudouridylation sites that could be potentially guided by E1, E2 or E3 snoRNAs [121] in the pre-rRNA segments known (by psoralen cross-linking) to interact with these snoRNAs in vivo [124]. The E1 RNA nucleotide positions that may psoralen cross-link in vivo to pre-rRNA [124] are not in sites that resemble the internal loop structures of the pseudouridylation pockets of pseudouridylation guide snoRNAs [121].

The molecule(s) that catalyzes the conversion to pseudouridine in eukaryotic pre-rRNA is unknown. Gar1p, a protein common to all yeast H/ACA snoRNAs, is needed for global pseudouridylation of pre-rRNA and stable association of H/ACA snoRNAs with pre-rRNA in yeast, but shares no conserved sequence motifs with pseudouridine synthases [26]. Cbf5p, a putative pseudouridine synthase, is present in all yeast H/ACA snoRNA-specific snoRNPs tested [27, 125]. Yeast cells lacking proteins Nhp2p and Nop10p are defective in global rRNA pseudouridylation, which may be the result of the unstable H/ACA snoRNAs present in these cells [28].

Concluding remarks

The precise functions of various snoRNA species in different pre-rRNA processing, particularly cleavage, steps remains to be elucidated. Little is known about the identity and functions of the proteins that interact with snoRNAs and how these interactions occur. Nothing is known about the functional interactions between different snoRNA species. It is not clear if even all the functional types of snoRNAs have been identified. Thus, many key questions remain unanswered about the snoRNPs in the molecular machine that produces the ribosomal subunits. The nucleolus has other functions in addition to those in rRNA biosynthesis and ribosomal subunit assembly. Several observations suggest that the nucleolus participates in the processing or nuclear export of some mRNAs; recent results indicate that the nucleolus is involved in the maturation of U6 spliceosomal snRNA, processing and/or ribonucleoprotein assembly of the signal recognition particle RNA, biosynthesis of the telomerase ribonucleoprotein (the enzyme that synthesizes chromosome ends) and processing of precursors of some transfer RNA (tRNA) species (reviewed in [126]). (It is interesting that there is an essential H/ACA snoRNA-like domain at the 3′ end of human telomerase RNA [127]). The study of these processes may reveal novel snoRNAs and/or new functions of the known snoRNAs. The recent unexpected findings about snoRNAs, as well as the important unanswered questions, suggest exciting years to come in the study of snoRNAs.

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