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REVIEW

RNA modification in Cajal bodies

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ABSTRACT

Aside from nucleoli, Cajal bodies (CBs) are the best-characterized organelles of mammalian cell nuclei. Like nucleoli, CBs concentrate ribonucleoproteins (RNPs), in particular, spliceosomal small nuclear RNPs (snRNPs) and small nucleolar RNPs (snoRNPs). In one of the best-defined functions of CBs, most of the snoRNPs are involved in site-specific modification of snRNAs. The two major modifications are pseudouridylation and 2′-O-methylation that are guided by the box H/ACA and C/D snoRNPs, respectively. This review details the modifications, their function, the mechanism of modification, and the machineries involved. We dissect the different classes of noncoding RNAs that meet in CBs, guides and substrates. Open questions and conundrums, often raised and appearing due to experimental limitations, are pointed out and discussed. The emphasis of the review is on mammalian CBs and their function in modification of noncoding RNAs.

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Introduction

Although many functions have been ascribed to Cajal bodies (CBs), perhaps the best-established function is that as sites of modification of spliceosomal small nuclear RNAs (snRNAs). Whereas other potential functions are covered in other sections of this Special Focus on CBs, this review will concentrate on the role of CBs in the modification of noncoding RNAs. Other aspects of CBs are covered in other sections.

Over the past few years, RNA modification has garnered some limelight mainly due to technical improvements of detection of the modifications enabling genome-wide approaches. For example, the identification of enzymes that remove N^6-methyladenosines from mRNAs showed the modification to be reversible and led to the development of methods identifying this modification genome-wide.[18,30,63] This precipitated exciting findings on the function and mechanism of this most abundant internal modification of mRNA.[49] In turn, this bounty of information stimulated interest in developing techniques for identification of other modifications that were long known in abundant noncoding RNAs, but technically inaccessible in mRNA. Thus, 4 independent studies identified pseudouridines in yeast and mammalian mRNAs showing that this modification is much more widespread than previously appreciated.[8,48,51,74] Despite the considerable interest and potential impact of these findings in mRNAs,[47] pseudouridines (and 2′-O-methyl groups) in noncoding RNAs far outnumber those in mRNAs for 2 reasons: first, ribosomal RNAs (rRNAs), snRNAs, and small nucleolar RNAs (snoRNAs) are orders of magnitude more abundant than mRNAs and, second, they each carry multiple modifications. It is perhaps for this reason that the sites of modification of these RNAs occupy specific organelles in the nucleus, nucleoli and CBs. Unless specified otherwise, this review focuses on modification events in mammalian CBs.

Overview

This brief overview is intended to make the subject more accessible to the uninitiated and serve as reference for the remainder of the review. Based on common sequence motifs and secondary structures, snoRNAs form 2 major families, box H/ACA and box C/D snoRNAs (Fig. 1A).[14,39] H/ACA and C/D RNAs each associate with their own set of the same 4 core proteins (Fig. 1A) to generate the functional units, small nucleolar ribonucleoproteins (snoRNPs). As the names suggest, the most abundant RNAs function in nucleoli (snoRNAs) and in CBs (small CB-specific, scaRNAs), where they guide the modification of rRNAs and snRNAs, respectively (Fig. 1B). A large, but low-abundant class of H/ACA RNAs is that of the AluACA RNAs, derived from intronic Alu elements (Fig. 1A).[29] Whereas most snoRNAs are expressed from introns of mainly housekeeping genes (Fig. 1B, a), a prominent H/ACA RNA, human telomerase RNA (hTR), and 5 abundant C/D RNAs (U3, U8, U13, mgU2-25/61, mgU12-22/U4-8) are expressed from their own RNA polymerase II promoters (Fig. 1B, b).[64,70,80,81,98] These independently expressed snoRNAs traffic through CBs, where apparently their 5′-cap is hypermethylated. The major modification targets in CBs, the spliceosomal snRNAs, are also independently expressed (Fig. 1B, c). However, most snRNAs then embark on an obligate cytoplasmic journey during which their 5′-cap is hypermethylated, their 3′-end is trimmed, and they assimilate Sm proteins for reimport into nuclei and trafficking to CBs

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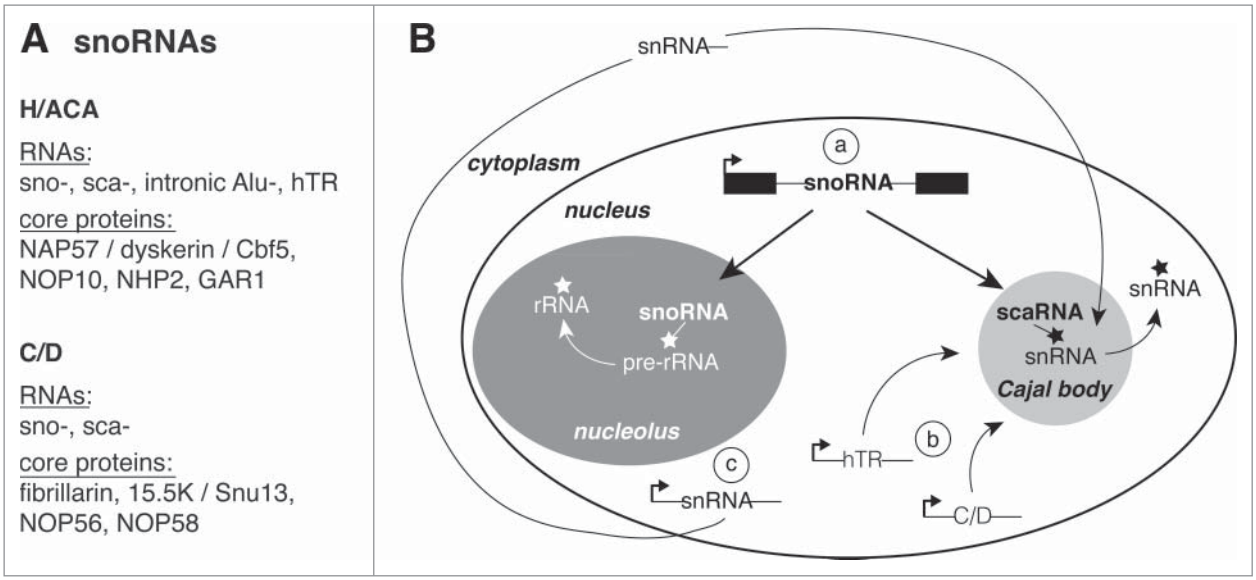

Figure 1. SnoRNAs and life cycle. (A) List of small nucleolar RNAs (snoRNAs) and ribonucleoprotein (RNP) core proteins. Abbreviations: small Cajal body (CB)-specific (sca) and human telomerase RNA (hTR). (B) Schematic of snoRNA mode of expression, trafficking, and sites of action and that of its main target in CBs, spliceosomal small nuclear RNAs (snRNAs). See text for full explanation. Pseudouridylation and 2′-O-methylation modifications are indicated (asterisks). Note proteins were left off for simplicity and clarity.

(Fig. 1B). Armed with this information, we can now delve into the nuts and bolts of CB function in RNA modification.

The modifications

Two modifications predominate in snRNAs and have been associated with CBs, pseudouridylation and 2′-O-methylation. Pseudouridylation is the isomerization of uridine to pseudouridine by breaking the N-glycosidic bond, followed by a 180° rotation of the base, and the formation of a C–C-glycosidic bond (Fig. 2A). 2′-O-methylation is the methylation of the 2′-hydroxyl group of the ribose moiety of any ribonucleoside (Fig. 2A). Both modifications change the biophysical properties of the RNA, even if to a minor degree. Compared to uridine, pseudouridine stabilizes base stacking, rigidifies the backbone (through coordination of a water molecule by the additional amino group of the base), and is more polar.[1,4,13] 2′-O-methylation changes the hydration shell around the oxygen and protects the RNA against alkaline hydrolysis.[5,23] As a consequence, modifications fine-tune the function of substrate RNAs.

Spliceosomal snRNAs harbor additional modifications. Except snRNA U6 and U6atac, all snRNAs possess a trimethylguanosine cap structure followed by two 2′-O-methylated residues that are modified during cap formation. One or two N^6-methyladenosines and 2-methylguanosines have also been identified in snRNAs.[58] However, these modifications do not occur in CBs. For example, cap hypermethylation occurs during the cytosolic step of U snRNP maturation (Fig. 1B).[61] Surprisingly, the cap methylase Tgs1 is also concentrated in CBs, where it may specifically hypermethylate the cap of independently expressed snoRNAs (Fig. 1B, b).[21,85] Similar to Tgs1, the survival of motor neurons protein (SMN), which functions in the cytoplasm to assemble Sm rings on snRNAs, also concentrates in CBs despite snoRNAs being devoid of Sm proteins.[50] Obviously, some aspects of the snRNP lifecycle and CB function remain to be elucidated.

Guide RNAs

To appreciate the role of CBs in RNA modification, it is important to understand the mechanism of modification. Although pseudouridylation and 2′-O-methylation can be catalyzed by single-protein enzymes, the modification of mammalian snRNAs appears exclusively accomplished by snoRNPs. Some of the snoRNPs have distinctive features and names (see below).[32,52,60,91] SnoRNPs each consist of a short, function-defining guide RNA and 4 core proteins including the pseudouridine synthase or the methyltransferase (Fig. 1A). Conserved sequence motifs characterize the guide RNAs, boxes H (ANANNA) and ACA in pseudouridylation guides and boxes C/C' (RUGAUGA) and D/D' (CUGA) in methylation guides (Fig. 2B and C). Base pairing of the guide RNAs with the substrate RNAs determines the nucleotides to be modified (Fig. 2B and C). Accordingly, each modification site possesses at least one complementary guide RNA. A large number of guide RNAs thus mirrors the large number of modification sites. Presently, some 700 snoRNAs are expressed at significant levels.[32] As the name suggests, the most abundant RNAs are localized in nucleoli where they function in the modification of rRNA, which contains about 100 of each modification that are all guided by snoRNAs.[56]

Guide RNPs

Each snoRNA is stabilized by 4 core proteins, box C/D RNAs by Nop56, Nop58, 15.5K, and the methylase fibrillarin and box H/ACA RNAs by NHP2, NOP10, GAR1, and the pseudouridine synthase NAP57, also known as dyskerin and Cbf5.[52,60,87]

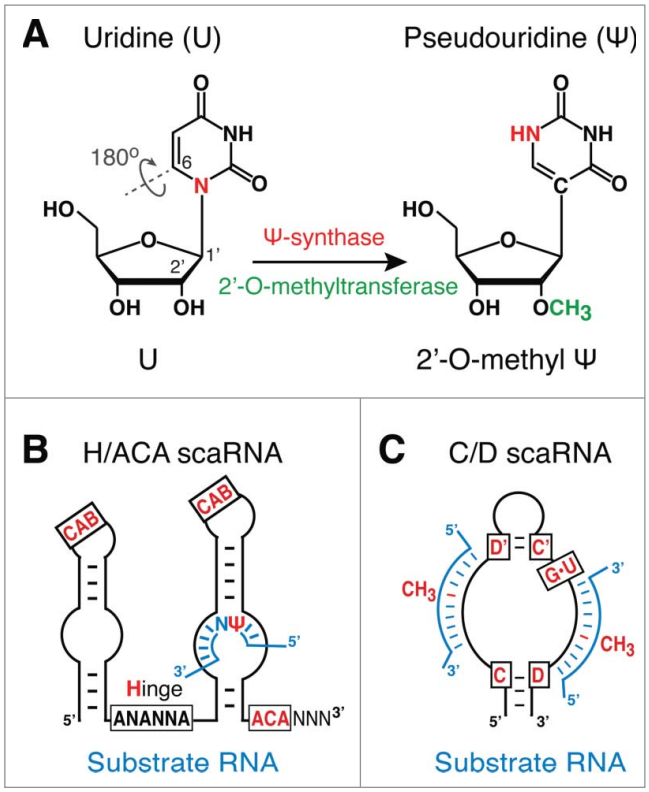

Figure 2. Modifications and scaRNAs. (A) Schematic of pseudouridylation (red) and 2′-O-methylation (green). Note although indicated on the same nucleoside, these are independent modification reactions. (B) H/ACA scaRNA with CB localizing elements (CAB) and a substrate RNA in one of the 2 pseudouridylation pockets. Note CAB boxes and guide elements can reside in one or the other hairpin or both. (C) C/D scaRNA with a CB localizing G•U/U•G wobble stem (G•U) and 2 substrate RNAs. Note the fifth nucleotide of the substrate from boxes D and/or D′ is targeted for 2′-O-methylation (CH_3).

Each RNP contains 2 sets of the core proteins, one for each kink-turn motif formed by boxes C/D and C'/D' and one for each hairpin of H/ACA RNAs. Although most individual snoRNAs are low-abundant and consequently difficult to detect in cells, collectively, they are readily identified through their core proteins by indirect immunofluorescence. In fact, the 2 enzymes of the RNPs, fibrillarin and NAP57, were among the first proteins identified in CBs, colocalizing with the CB marker coilin.[2,62,69]

Substrate RNAs

The identification of coilin afforded the immunolocalization in CBs of trimethylguanosine capped RNAs, Sm proteins, and the U1 snRNP.[68,76] These RNAs corresponded to the spliceosomal snRNAs U1, U2, U4, and U5 whose concentration in nuclear foci was visualized around the same time by RNA fluorescent in situ hybridization (FISH).[10] After a cytoplasmic maturation phase – where they acquire a heptameric ring of Sm proteins, their cap is hypermethylated, and their 3′-end is trimmed – mammalian snRNAs reenter the nucleus and shuttle to CBs, possibly with the help of the cap hypermethylase Tgs1 and the Sm assembly protein SMN.[61,66,79,84,86] In addition to snRNAs, the snoRNAs U3 and U8 target to CBs.[42,43,44,65,73] All these noncoding RNAs are subject to pseudouridylation and 2′-O-methylation. Spliceosomal snRNAs collectively contain 28 pseudouridines and 18 2′-O-methyl groups (Table 1).[33,58,93] At least in the case of U2 snRNA, which contains 13 pseudouridines alone, the modifications are essential for snRNP formation and splicing.[92] Further, the perhaps most prominent H/ACA RNA, human telomerase RNA (hTR), accumulates in CBs.[27,97] The hTR of active telomerase RNPs is pseudouridylated and its modification affects the structure of the RNA and the function of telomerase.[36] Apparently, all snoRNA substrates are independently expressed and it remains to be determined if intronic snoRNAs are also modified.

Small CB-Specific RNAs – scaRNAs

The guide RNAs responsible for snRNA modification are specialized snoRNAs in CBs, the small CB-specific RNAs (scaRNAs). Although they possess all the features of common box H/ACA and C/D RNAs, they harbor additional short sequence motifs that are responsible for CB localization, in case of H/ACA RNAs, it is the CAB box (ugAG) and in that of C/D RNAs, it is the G•U/U•G wobble stem (Fig. 2B and C).[57,71] The CAB box is recognized by the WD40 repeat protein Wdr79 (aka Wrap53 and TCAB1) that is required for localization of scaRNPs to CBs.[82,83] Although C/D scaRNAs lack a CAB box, Wdr79 is also involved in their targeting to CBs even if it recognizes these scaRNAs with a G•U/U•G wobble stem about 20-fold less than H/ACA scaRNAs with a CAB box.[82]

In addition to these sequence motifs required for CB localization, some scaRNAs show remarkable features not seen in other snoRNAs. They can occur as tandem snoRNAs with 4 potential guide sequences instead of 2 and they can form hybrid snoRNAs, wherein an H/ACA RNA with a CAB box is inserted into the loop of a C/D snoRNA giving rise to 2 potential pseudouridylation pockets and 2 methyl guide sequences (Table 2).[11,26,38] Currently 29 scaRNAs have been described, 17 H/ACA, 2 C/D, 1 tandem H/ACA, 4 tandem C/D, and 5 hybrid C/D-H/ACA scaRNAs (Table 2).[32] Additionally, hTR, which carries a CAB box and ends in an H/ACA domain, is a scaRNA running up the current number of scaRNAs to 30.[27,64] If we consider the expression levels of the scaRNAs reported in the ENCODE sRNA-seq data,[32] then the H/ACA motifs outnumber the C/D motifs over 20-fold. Consequently, box H/ACA core proteins should outnumber box C/D core proteins more than 20-fold in CBs because scaRNAs concentrate in CBs and

Table 1. Number of human internal snRNA modifications.

snRNA	U1	U2	U4	U5	U6	U4atac	U6atac	U12	Total
Pseudouridines*	2	13	3	3	3	1	1	2	28
2′-O-methyl groups*	1	7	2	2	5			1	18

*Numbers are from.[33,58,93]

Table 2. List of scaRNAs.

Name	Alt. Name	ID	Type	Target 1	Target 2	Target 3	Target 4
SCARNA7	U90	snoID_0598	CD-SCARNA	5.8S-76	U1.1-70		
SCARNA28		snoID_0620	CD-SCARNA	U2.2-47	NA		
SCARNA1	ACA35	snoID_0603	HACA-SCARNA	NA	18S-1441		
SCARNA3	HBI-100	snoID_0596	HACA-SCARNA	NA	U6.6-40		
SCARNA4	ACA26	snoID_0595	HACA-SCARNA	U2.3-41	U2.3-39		
SCARNA8	U92	snoID_0601	HACA-SCARNA	U2.3-34	U2.3-44		
SCARNA11	ACA57	snoID_0610	HACA-SCARNA	NA	U5.3-41		
SCARNA14	U100	snoID_0612	HACA-SCARNA	NA	U1.1-72		
SCARNA15	ACA45	snoID_0604	HACA-SCARNA	NA	U2.3-39		
SCARNA16	ACA47	snoID_0602	HACA-SCARNA	NA	U1.4-5		
SCARNA18	U109	snoID_0609	HACA-SCARNA	NA	U1.4-6		
SCARNA18B		snoID_0707	HACA-SCARNA	NA	U1.4-6		
SCARNA19	hTR/TERC	snoID_1118	HACA-SCARNA	telomeres			
SCARNA20	ACA66	snoID_0592	HACA-SCARNA	NA	U12.1-27		
SCARNA21B		snoID_0577	HACA-SCARNA	U12.1-18	28S-4426		
SCARNA22	ACA11	snoID_0611	HACA-SCARNA	NA	NA		
SCARNA23	ACA12	snoID_0594	HACA-SCARNA	NA	U6.6-40		
SCARNA26A		snoID_0618	HACA-SCARNA	U4.2-79	NA		
SCARNA26B		snoID_0625	HACA-SCARNA	U4.1-79	NA		
SCARNA27		snoID_0614	HACA-SCARNA	NA	NA		
SCARNA5	U87	snoID_0597	Hybrid	U5.1-39	18S-595	18S-1530	U4.1-65
SCARNA6	U88	snoID_0613	Hybrid	U5.1-39	18S-1628	28S-2861	28S-1530
SCARNA10	U85	snoID_0608	Hybrid	18S-283	U5.1-44	1818S-101	U5.1-43
SCARNA12	U89	snoID_0607	Hybrid	NA	18S-917	18S-556	18S-464
SCARNA21	ACA68	snoID_0599	Hybrid	U12.1-17	U12.1-18	U6atac-83	28S-4426
SCARNA2	HBII-382	snoID_0593	Tandem-CD	U2.1-25	NA	18S-1363	28S-1963
SCARNA9	mgU2-19/30	snoID_0605	Tandem-CD	U2.1-19	NA	NA	U2.1-30
SCARNA9L		snoID_0600	Tandem-CD	U2.1-19	NA	NA	U2.1-30
SCARNA17	U91	snoID_0591	Tandem-CD	U12-21	NA	U4.1-8	U2.1-43
SCARNA13	U93	snoID_0606	Tandem-HACA	NA	U7-7	U5.1-51	U2.3-54

Data from[32] except the alternative (alt.) names.[46]
The predicted targets refer to the snRNAs and rRNAs followed by target nucleotide position.

the snoRNP core proteins assemble proportionately around each motif. Indeed, relative to nucleoli, the indirect immunofluorescence signal for NAP57 is higher in CBs, whereas that for fibrillarin is consistently lower than in nucleoli.[62,69] However, it should be noted that some of the scaRNAs have reported targets in both, CBs and nucleoli (Table 2). Although, the targets need to be experimentally verified, these scaRNAs are therefore likely residents of both nuclear bodies. Thus it seems that even in the case of scaRNAs, there is no absolute separation between nuclear organelles.

Where substrate and guide RNAs meet – A function for CBs

Given the congregation of modification machinery and substrate RNAs in CBs, it was a small step to predict that CBs are the sites of snRNA modification – guilty by association. Demonstration of this theory however was not straightforward. The elegant work of the Kiss group pointed the way.[28] First, they showed that a mutant U2 snRNA that is unable to reenter the nucleus indeed failed to be modified. Only when targeted to CBs, but not to nucleoli, was U5 snRNA modified documenting that CBs are the sites of snRNA modification. For other potential functions of CBs, such as RNP assembly, the reader is referred to other reviews of this Special Focus issue. Modification of snRNAs, however, can also occur in the absence of CBs, i.e. in coilin knockout cells, which are left with 2 types of remnants of CBs, one that accumulates the scaRNAs and snRNAs and one that accumulates independently transcribed snoRNAs and the snoRNP chaperone Nopp140, hinting at a separation of snRNA and snoRNA modification.[28,79] That CB structures per se are not required for snRNA modification is further supported by data from fly, which, when lacking CBs and Wdr79 still contain fully modified snRNAs.[15,16] Moreover, snRNA modification can occur in the absence of SMN.[17] Finally, even mammalian cells often do not contain visible CBs, yet their pre-mRNA splicing seems unperturbed.[76] Obviously, snRNAs and scaRNPs can get together without the environs of CBs.

On the other hand, the number and size of CBs correlates positively with the metabolic rate of the cell including transcription and with it pre-mRNA splicing and snRNA synthesis and modification.[40,45,75,77] Altogether, these findings support a model whereby, through concentration of snRNAs and scaRNPs, CBs promote snRNA modification, which can also occur outside of these bodies even if at lesser efficiency.

Alternative methods of modification and consequences

Although snRNA modification in mammalian cells appears exclusively catalyzed by scaRNPs, in yeast there are 2 mechanisms, an RNA-guided and an RNA-independent, i.e., protein-only, mechanism.[53,54] Whether the latter exists in mammalian cells is not clear, though a recombinant Pus7 homolog is capable of pseudouridylating the uridine in position 34 of human U2 snRNA and a redundant modification mechanism was indicated.[33,96] Alternatively, the absence of a true CB (and with it scaRNAs) in yeast could account for the difference. It will be interesting to determine if mammalian snRNA modification can be induced at novel sites as demonstrated for yeast snRNAs and if such modification would also occur in CBs.[89] These are important questions, as modification of snRNAs can have

serious consequences. Thus, modification is generally required for snRNP assembly and pre-mRNA splicing.[92] And specifically, pseudouridines in U2 snRNA stimulate the ATPase activity of Prp5 during spliceosome assembly and a pseudouridine in U6 snRNA is part of the filamentous growth program in yeast.[7,88] In mRNA, pseudouridines can turn nonsense codons into sense codons diversifying the cellular proteome?[34]

Open questions

Though the function of CBs as sites of snRNA modification is firmly established, many questions and puzzles remain. For example, are all snRNAs modified in CBs, what about U6, which lacks a trimethylguanosine cap, does not transit through the cytoplasm, and which was proposed to be modified in the nucleolus?[20,94]

Regardless, the pseudouridylation of at least one of its uridines is catalyzed by a scaRNP – scaRNA23 guides the pseudouridylation at position 40 of U6 snRNA.[37]

What about snoRNAs, do all traffic through CBs? Unlike most other snoRNAs, U3 and U8 are highly abundant and thus could be isolated and their modification directly demonstrated,[35,70] but no guide RNAs have been identified so far.[32,46] Whether other, less abundant snoRNAs are modified is unknown. After transfection or microinjection, U3, U8, and U14 snoRNAs indeed traffic to or through CBs, but, except for U3 snoRNA,[31,67] endogenous molecules have so far escaped detection in CBs.[9,10,65,66,73] In contrast, the endogenous scaRNAs U85, U88, U91, and U92 have been visualized in CBs.[11]

Regardless, the identification of most snoRNAs among RNAs UV-crosslinked to coilin would suggest that most snoRNAs, if not all, traffic through CBs.[55] Indeed, after microinjection some of these snoRNAs are detected in CBs before accumulating in nucleoli, their place of action. Nevertheless, whereas coilin is highly concentrated in CBs, some 70% of it is present in the nucleoplasm, even if much more dilute.[3,9,41,59] Therefore, it cannot be excluded that some of the snoRNA associations with coilin occur outside CBs. If CBs play a role in the biogenesis of all snoRNPs, then why are none of the snoRNP maturation factors, except Nopp140, present in CBs?[12,22,24] Importantly, assembly of most core proteins, at least in the case of H/ACA RNPs, does not occur in CBs but at the site of snoRNA transcription.[6,12,19,72,90] Finally, it is unclear how all the snoRNPs involved in rRNA modification find their way into CBs without specific localizing motifs.

To what degree are snRNAs modified? The simple fact that snRNA modifications were recognized early on suggests that most of the snRNAs are fully modified at individual sites. Indeed, this has been verified for the case of yeast rRNA using a quantitative mass spectrometric approach showing that some 84% of the 112 modified nucleotides are nearly fully modified.[78] This is in stark contrast to genome-wide RNAseq based approaches that identified much lower levels of, e.g., pseudouridylation.[95] Thus, it can be safely assumed that most modification positions in snRNAs are modified to a high degree.

Furthermore, there is the conundrum of how the different types of RNAs find their way into CBs. While there seems to be a role for Tgs1 and SMN in targeting of snRNAs and for PHAX in targeting of snoRNA substrates to CBs,[84] how the remainder of the snoRNPs find their way into CBs remains unclear. In contrast, accumulation of scaRNAs clearly depends on their CAB box that is recognized by Wdr79, but CAB boxes are also present in the over 300 AluACA RNAs that are present in the nucleoplasm but not CBs.[29] Therefore, although necessary, Wdr79 may not be sufficient for targeting of scaRNAs but require additional factors, perhaps such as the nucleolar and CB protein Nopp140.[25] Obviously, these are only some of the questions that remain to be clarified, leaving plenty of CB modification work ahead.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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