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REVIEW

Assembly and trafficking of box C/D and H/ACA snoRNPs

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ABSTRACT

Box C/D and box H/ACA snoRNAs are abundant non-coding RNAs that localize in the nucleolus and mostly function as guides for nucleotide modifications. While a large pool of snoRNAs modifies rRNAs, an increasing number of snoRNAs could also potentially target mRNAs. ScaRNAs belong to a family of specific RNAs that localize in Cajal bodies and that are structurally similar to snoRNAs. Most scaRNAs are involved in snRNA modification, while telomerase RNA, which contains H/ACA motifs, functions in telomeric DNA synthesis. In this review, we describe how box C/D and H/ACA snoRNAs are processed and assembled with core proteins to form functional RNP particles. Their biogenesis involve several transport factors that first direct pre-snoRNPs to Cajal bodies, where some processing steps are believed to take place, and then to nucleoli. Assembly of core proteins involves the HSP90/R2TP chaperone-cochaperone system for both box C/D and H/ACA RNAs, but also several factors specific for each family. These assembly factors chaperone unassembled core proteins, regulate the formation and disassembly of pre-snoRNP intermediates, and control the activity of immature particles. The AAA+ ATPase RUVBL1 and RUVBL2 belong to the R2TP co-chaperones and play essential roles in snoRNP biogenesis, as well as in the formation of other macro-molecular complexes. Despite intensive research, their mechanisms of action are still incompletely understood.

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Introduction

SnoRNAs (smal nucleolar RNAs) are a well studied class of non-coding RNAs that localize in nucleoli. Based on conserved sequence elements, they are classified into box C/D or box H/ACA snoRNAs (Fig. 1). These RNAs function in the site-specific ribose 2′-O-methylation and pseudouridylation of target RNAs, respectively, and they exist in a variety of organisms, from archea to higher eukaryotes.[1,2] A vast majority of them have sequence complementarity to rRNA (rRNA) and guide nucleotide modifications in the nucleolus. These modifications often cluster in functionally important regions of the ribosome.[3] A subset of H/ACA and C/D snoRNPs is also required for pre-rRNA cleavage steps.[4] SnoRNPs can also target other RNAs. In higher eukaryotes, U6 small nuclear RNA (snRNA) modifications are guided by several snoRNAs.[5] A role of snoRNPs in mRNA modifications has also been proposed early on.[6] Recently, genome-wide mapping of RNA modification sites[7] or genome-wide mapping of RNA-RNA interaction sites raise the hypothesis that at least some modifications within mRNAs may be snoRNA-guided.[8,9] Some snoRNAs are also believed to regulate alternative splicing of pre-mRNAs.[10,11] In addition to the canonical snoRNAs, cells contain a number of related families. ScaRNPs (small Cajal body-specific RNAs) can adopt a C/D or H/ACA fold but they contain additional elements that retain them in Cajal bodies (CBs), and many of them target modifications of spliceosomal snRNAs (small nuclear RNAs).[12] ScaRNPs can either contain a pair of box H/ACA or a pair of box C/D motifs, or they can be composite guide RNAs containing the 2 motifs at the same time.[13,14] Interestingly, the vertebrate telomerase RNA that functions in telomeric DNA synthesis[15] resembles scaRNAs and also localizes to CBs.[16,17] This RNA however leaves CBs to accumulate at certain telomeres in S-phase. Another recently characterized family is the one of AluACA RNAs.[18] These RNAs of unknown function are derived from Alu elements and fold into a structure that is similar to that of H/ACA scaRNAs, although they localize in the nucleoplasm rather than in CBs.

For both the C/D and H/ACA families, a set of core proteins associates with the snoRNA to form a stable and functional snoRNP particle (reviewed in[19,20]). For C/D snoRNAs, these are SNU13 (15.5kD), the 2 highly related proteins NOP56/NOP58 and the methyltransferase FBL (also named Fibrillarin, or in yeast Nop1p; Table 1). For H/ACA snoRNAs, the core proteins are NHP2, NOP10, GAR1 and the pseudouridine synthase DKC1 (Dyskerin, or Cbf5p in yeast; Table 1). Core proteins are essential for viability in the yeast *S. cerevisiae*. Assembly with core proteins is also required for the nucleolar localization of snoRNAs in both yeast and human.[21,22] The assembly of box C/D and H/ACA RNPs is a multistep mechanism that requires numerous factors and displays a surprising spatio-temporal complexity. These stepwise processes could serve as quality-control mechanisms during the formation of H/ACA and C/D snoRNPs.

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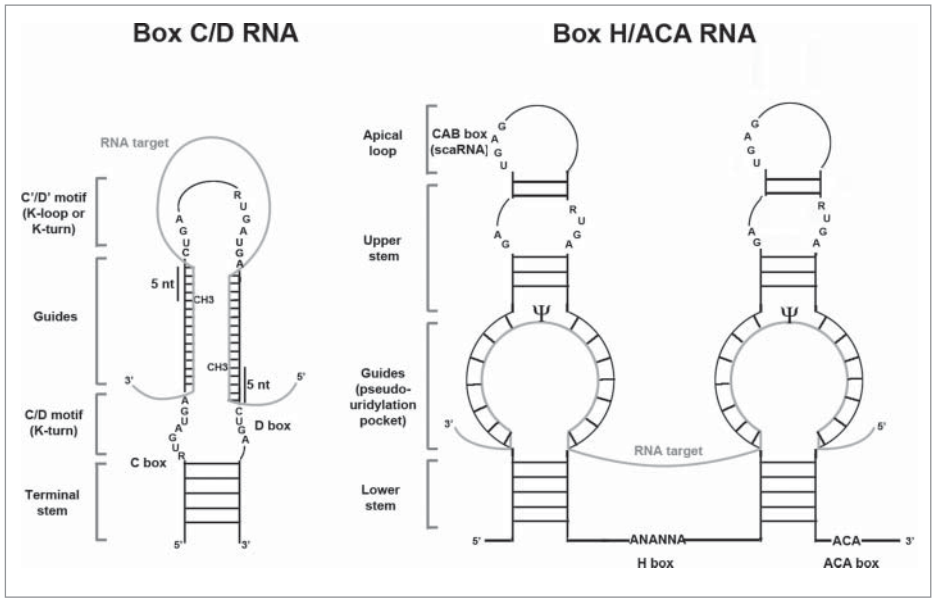

Figure 1. Structures of box C/D and H/ACA RNAs. (A) Secondary structure of a typical box C/D RNA. Consensus boxes called C, D, C′ and D′ pair to form box C/D and box C′/D′ which are folded into kink-turn and kink-loop respectively. The D and D′ boxes and their juxtaposed sequences are complementary to the target RNA, and the methylated nucleotide is the fifth nucleotide upstream of D or D′ boxes. (B) Secondary structure of a typical box H/ACA RNA. Each hairpin is composed of a lower stem, a bulge known as the pseudouridylation pocket, an upper stem and an apical loop. Hairpins are separated by the H box and the last hairpin contains an ACA box at its 3′end. The Ψ Pocket has sequence complementarity to the target RNA. The uridine to be isomerized is located under the upper stem. ScaRNAs specifically contain a CAB box which allows the RNA to be retained in CBs.

Table 1. Core proteins of snoRNPs and factors involved in their biogenesis.

Protein category	Protein Vertebrate	Budding yeast	Feature	Localisation
Core Box C/D RNP proteins	SNU13	Snu13p	L7Ae family	CBs, Nucleoli
	FBL	Nop1p	Methyltransferase	CBs, Nucleoli
	NOP56	Nop56p	NOP domain	CBs, Nucleoli
	NOP58	Nop58p	NOP domain	CBs, Nucleoli
Core Box H/ACA RNP proteins	NHP2	Nhp2p	L7Ae protein	CBs, Nucleoli
	DKC1	CbfSp	Pseudouridine synthase	CBs, Nucleoli
	GAR1	Gar1p	GAR domain	CBs, Nucleoli
	NOP10	Nop10p		CBs, Nucleoli
Assembly factors	HSP90		Chaperone	nucleoplasm, cytoplasm
	RPAP3	Tah1p	R2TP, TPR, RPAP3 Cter	nucleoplasm, cytoplasm
	PIH1D1	Pih1p	R2TP, PIH domain	nucleoplasm, cytoplasm
	RUVBL1	Rvb1	R2TP, AAA+ ATPase	nucleoplasm, cytoplasm
	RUVBL2	Rvb2	R2TP, AAA+ ATPase	nucleoplasm, cytoplasm
	NUFIP	Rsa1p	PEP domain, Zinc finger	nucleoplasm, cytoplasm
	ZNHIT3	Hit1p	HIT Zinc finger	nucleoplasm, cytoplasm
	ZNHIT6	Bcd1p	HIT Zinc finger	nucleoplasm, cytoplasm
	C12orf45	/	uncharacterized	nucleoplasm, cytoplasm
	NAF1	Naf1p	GAR domain	nucleoplasm
	SHQ1	Shq1p	CHORD and Sgt1 (CS) domains	nucleoplasm
	IBP160		SF1 family of RNA helicase	speckles
RNA processing	TGS1	Tgs1p	Hypermethylase	cytoplasm, CBs
	La	Lhp1p	La domain	nucleoplasm
	MTR4	Mtr4p	RNA helicase	nucleoplasm, nucleoli
	RRP6	Rrp6p	Exonuclease	nucleoplasm, nucleoli
	RRP47	Rrp47p	Nucleic acid binding protein	nucleoplasm, nucleoli
	XRN2	Xrn2p	Exonuclease	nucleoplasm, nucleoli
	PAPD5	/	PolyA-RNA polymerase	nucleoli, CBs
	PARN	/	PolyA-specific ribonuclease	nucleoli, CBs
RNA localization	PHAX	/	Adaptator to CRM1	Nucleoplasm
	Ran		GTPase	Nucleoplasm
	CRM1	Crm1p	Export receptor	CBs, Nuclear enveloppe
	NOPP140	Srp40p	Shuttling protein	CBs, Nucleoli
	Coilin	/	RG rich domain	CBs
	SMN	/	Tudor domain	cytoplasm, CBs/gems
	WDR79		WD40 domain	cytoplasm, nucleoplasm enriched in CBs

SnoRNA maturation is coupled with assembly of core proteins

Most vertebrate snoRNAs are encoded within introns of pre-mRNAs.[23-26] Human box C/D snoRNAs have a preferential intronic location situated 50 nucleotides upstream of the branch-point[27] and IBP160, also called Aquarius, was proposed to couple recruitment of snoRNP core proteins with splicing of the host pre-mRNA.[28] Assembly of box C/D snoRNPs is generally dependent on splicing, although long external stems that facilitate folding of the snoRNAs can make the process splicing-independent.[29] Splicing of the host pre-mRNA generates a snoRNA precursor that is debranched and that has to be further processed by exonucleases.[30] Binding of core proteins is essential to protect the termini of mature snoRNAs from exonucleolytic degradation, and some core proteins are essential for the stability of mature snoRNAs.[31,32] Processing at the 5′-end requires exonucleases of the XRN1/2 families,[33] while processing at the 3′-end requires the RNA exosome and several adaptors such as the NEXT complex in human cells[34] or the RRP47 protein in yeast, which directly interacts with the C/D core protein NOP56/NOP58.[35] In the case of H/ACA snoRNAs, 3′-end processing has also been proposed to involve PAPD5-dependent adenylation and PARN-dependent 3′-end trimming.[36]

A few snoRNAs, as well as some scaRNAs and the telomerase RNA, are transcribed from their own promoter as independent transcripts. In these cases, the precursor transcripts are m^7G-capped and also carry 3′ extensions. Maturation at the 3′-end requires exonucleases as in the case of intronic snoRNAs, while maturation at the 5′-end occurs either via endonucleolytic cleavage, or via the formation of an hypermethylated $m^{2,2,7}$G cap (TMG) by the enzyme TGS1.[37] Hypermethylation is also coupled with assembly since TGS1 is recruited by the core proteins NOP56/NOP58 for C/D snoRNAs, and DKC1 for H/ACA snoRNAs.[37-39]

Assembly of snoRNPs requires the HSP90/R2TP chaperone system

Structural studies in the archaeal and eukaryotic systems have revealed that box C/D snoRNAs have a pseudo-dimeric shape organized around the C/D and C'/D' motifs.[40-44] *In vitro* experiments and structural data have also shown that SNU13 directly binds the K-turn of these motifs,[45] while the NOP domain of NOP56/NOP58 recognizes the RNP formed by SNU13 bound to the snoRNA, and also recognizes additional nucleotides of the C/D and C'/D' motifs.[43,46-49] The N-terminal domains of NOP56/NOP58 associate with the methyl-transferase FBL, while their coiled-coil domains heteromerize to allow communication between the C/D and C'/D' structural units. This interaction locks the RNP into the proper conformation,[42,43,50] and reviewed in.[20,51] Perturbation of the interface between NOP56 and NOP58 loosens the specificity of the methyltransferase reaction.[52]

NHP2 is a core protein of H/ACA snoRNPs that is related to SNU13, as both NHP2 and SNU13 belong to the L7Ae family of RNA-binding proteins.[53] However, NHP2 does not show specificity for K-turn motifs and appears to have a poor RNA-binding specificity.[54] In the H/ACA snoRNPs, NHP2 associates through protein-protein interaction with NOP10.[55] All box H/ACA RNAs share similar hairpin-hinge-hairpin-tail secondary structures (Fig. 1).[56,57] The single stranded hinge region contains the conserved H box. Another conserved sequence, the ACA box, is located in the tail, 3 nucleotides upstream from the 3′ termini of the RNAs. In the RNP, DKC1 interacts directly with the RNA, and NOP10 and GAR1 bind independently to 2 orthogonal faces of DKC1 catalytic domain.[55,58-62] In eukaryotes, all core proteins are required for optimal enzymatic activity, even though particle lacking NHP2 still presents a reduced activity,[62] and reviewed in.[63,64] GAR1 is believed to be essential for substrate turnover during the enzymatic reaction in both the archaeal and eukaryotic RNPs.[62,65-67]

Box C/D and H/ACA snoRNPs have unrelated structures, but recent studies have shown that the same machinery is involved in the assembly of these RNPs: the HSP90/R2TP chaperone-cochaperone system.[68-70] This system plays essential roles in the biogenesis of snoRNPs, and appears to use specific adaptors to interact with either C/D or H/ACA snoRNPs. The R2TP complex is composed of PIH1D1, RPAP3, and 2 AAA+ ATPase, RUVBL1 and RUVBL2 (Table 1). PIH1D1 and RPAP3 form a heterodimer in which RPAP3 directly contacts HSP90 while PIH1D1 associates with client proteins. RUVBL1/2 form a heterohexamer that makes ATP-dependent contacts with clients as well as with the PIH1D1:RPAP3 heterodimer.

The R2TP complex was first described in yeast[71] and later found in human cells, where it associates with an additional set of prefoldin proteins.[68,72,73] RUVBL1 and RUVBL2 were identified early on by proteomic studies of *in vitro* assembled C/D snoRNPs.[74] Depletion of the yeast homolog of RUVBL2 leads to a loss of both box C/D and box H/ACA snoRNAs, and to a defect in the trafficking of snoRNP proteins to the nucleolus.[75] In addition, the ATPase activity of RUVBL2 appears to be required for these activities. The involvement of the yeast R2TP complex in box C/D snoRNP assembly was further supported by the finding that yeast PIH1D1 interacts with yeast NOP58,[76] and by the fact that depletion of the yeast homologs of PIH1D1 and RPAP3 confers a temperature-sensitive phenotype where box C/D snoRNP biogenesis is mildly affected under normal growth condition and more strongly under stress conditions.[68,69,77]

Interestingly, the HSP90/R2TP system was later shown to be involved in the formation of other macromolecular complexes: the snRNP U4;[78] the RNA polymerases;[79] and complexes containing one of the 6 PIKKs (mTOR, ATM/ATR, DNA-PK, SMG1 and TRRAP) (reviewed in[80,81]). Therefore the HSP90/R2TP system appears to be an unusual chaperone that is specialized in the assembly of macromolecular complexes, in particular those involved in gene expression and cell proliferation. This system thus plays essential roles in the cell, as also highlighted by its involvement in cancer (reviewed in[82]). The well-characterized and relatively simple organization of snoRNPs makes them a convenient model to understand the role HSP90/R2TP system in the formation of macromolecular complexes.

The assembly of box C/D snoRNPs

The box C/D assembly factors

The assembly of box C/D snoRNPs has been studied using a variety of approaches, and this allowed to characterize several assembly factors besides the R2TP complex:

- ZNHIT6, which was initially identified in a functional screen in yeast.[83] Yeast ZNHIT6 is an essential protein in yeast and it is required for the accumulation of box C/D snoRNPs. Its function is however still poorly characterized.
- NUFIP, which was found in a 2-hybrid screen, together with ZNHIT3.[68,84] ZNHIT3 forms an heterodimer with NUFIP and regulates its abundance in both yeast and human cells. In addition, the NUFIP:ZNHIT3 heterodimer can further associate with SNU13 to form a stable ternary complex *in vitro*.[85]
- C12orf45, which was recently found in a proteomic screen and was shown to tightly associate with NOP58.[84] Its function is not yet understood.

ZNHIT3 and ZNHIT6 are both involved in the assembly of C/D snoRNPs and, interestingly, these factors both belong to a small family of proteins characterized by the presence of an extended Zn-finger domain containing 7 cysteines and one histidine, called the HIT domain. The HIT domain of the yeast homolog of ZNHIT6 is required for cell growth and for the stability of box C/D snoRNAs under stress. It can however be interchanged with the HIT motif of ZNHIT3, indicating that although it is important functionally, it does not appear to carry a strong specificity.[86] Interestingly, there are 6 members of the ZNHIT family in human and 4 in yeast, and as noted previously,[87] these proteins appear to have intimate links with the ATPases RUVBL1 and RUVBL2. In particular, ZNHIT1 and ZNHIT4 are part of the INO80 and SRCAP chromatin remodeling complexes together with RUVBL1/2, and they appear to lie at the interface between RUVBL1/2 and the other subunits of these complexes.[88] ZNHIT proteins could thus function as adaptors between RUVBL1/2 proteins and their clients, and could also potentially regulate their ATPase activity.

Interestingly, the other assembly factors also interact with the R2TP complex: the NUFIP:ZNHIT3 heterodimer binds PIH1D1,[85] and C12orf45 interacts with RUVBL1.[84] These factors could thus act as adaptors between R2TP and core proteins or as regulators of R2TP activity.

The box C/D assembly pathway

Part of the assembly pathway of box C/D snoRNPs was deciphered using quantitative proteomic approaches in human cells.[84] This allowed to describe the formation of an early protein-only complex that contains the 2 core proteins SNU13 and NOP58, in association with the AAA+ ATPase RUVBL1/2 and the assembly factors NUFIP, ZNHIT3 and ZNHIT6 (Fig. 2).[84] Whether this protein-only complex forms in the cytoplasm or in the nucleus is currently not known but the formation of this complex appears to occur downstream of the HSP90/R2TP system.[84] In the R2TP complex, RUVBL1/2 are associated with PIH1D1-RPAP3, but only RUVBL1/2 are found in this early complex. Interestingly, only ATP-loaded RUVBL1/2 can bind to ZNHIT6, whereas the binding of ATP releases RUVBL1/2 from R2TP.[69,89] This would suggest that it is the ATP loaded form of RUVBL1/2 that binds the pre-snoRNP complex and that the role of the HSP90/R2TP system would thus be to liberate RUVBL1/2 from R2TP to load them on the core proteins

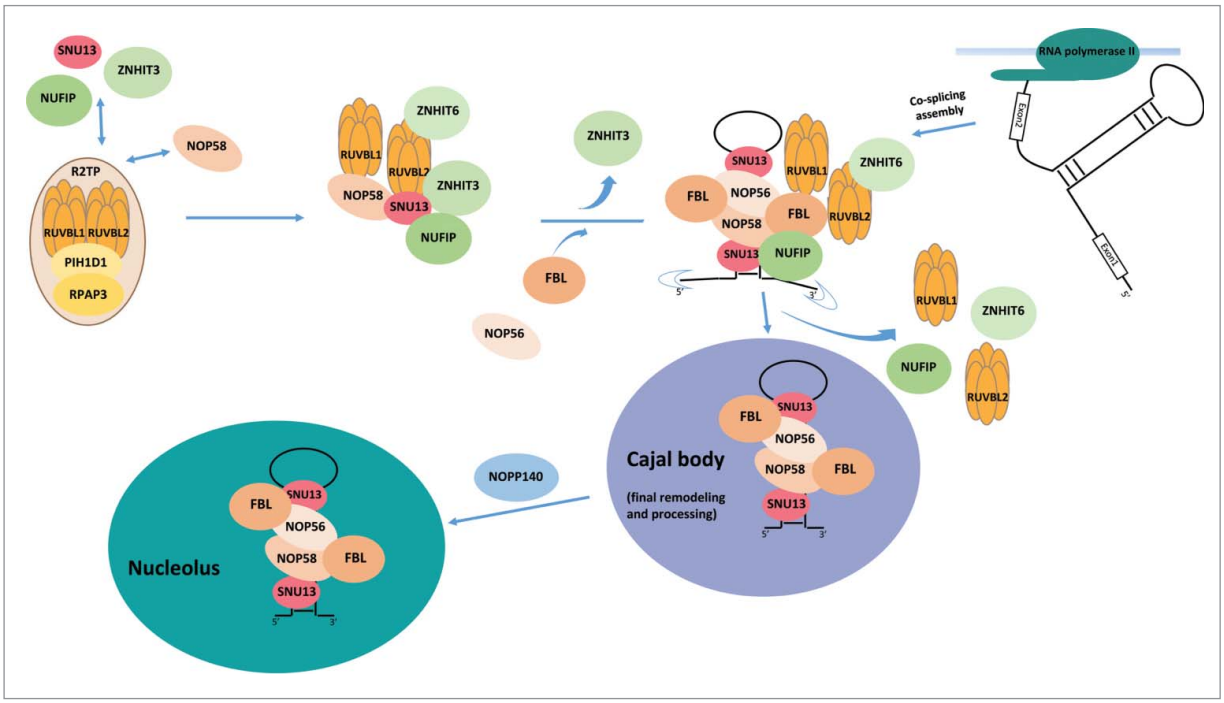

Figure 2. Assembly and trafficking of box C/D snoRNPs. During the biogenesis of box C/D snoRNPs, a protein only complex containing SNU13 and NOP58 is pre-formed with the help of HSP90/R2TP complex, and is loaded on snoRNA in a co-splicing manner. Pre-snoRNP particles are then transported to CBs where final processing occurs. It is not clear if assembly factors leave pre-snoRNP before or after arriving in CBs. Catalytically active snoRNPs are targeted to nucleoli where they function in ribose methylation on rRNAs. The blue symbols at the extremities of the RNA represent exonucleolytic enzymes.

SNU13 and NOP58.[84] In agreement with this idea, yeast NOP58 mutants that fail to assemble with SNU13 interact more strongly with yeast R2TP and in particular with the yeast homologs of PIH1D1 and RPAP3.[78]

Proteomic data indicate that in human cells, ZNHIT3 would be released upon binding of the protein-only complex to snoRNAs. In contrast, RUVBL1 and RUVBL2 were shown to interact with C/D snoRNAs and to remain in the pre-snoRNP complexes until the last stages of maturation.[74,90] Likewise, ZNHIT6 and NUFIP also become associated with box C/D snoRNAs during their biogenesis,[68,89] and structural data indicate that the interaction of NUFIP with SNU13 would prevent the premature formation of catalytic active snoRNPs, which may be deleterious for the cells.[84] The final steps of snoRNP maturation would thus require removal of RUVBL1/2, ZNHIT6 and NUFIP, which would in turn allow maturation into a catalytically active snoRNP particle.

Recruitment of core proteins to the HSP90/R2TP complex

While the late part of the assembly pathway of box C/D snoRNPs is relatively well described, the early steps are less characterized. In particular, it is not clearly understood how the core proteins NOP58 and SNU13 are recognized by HSP90 and the R2TP complex, although the PIH1D1:RPAP3 heterodimer is believed to play an important role in this process. Indeed, while RUVBL1/2 can directly interact with either NOP58 or SNU13,[89] these interactions are believed to be important at a later assembly steps, and not for the initial recruitment of these proteins to the R2TP complex.

A first question is whether HSP90 lies upstream or downstream of the R2TP complex. NOP58 and SNU13 become destabilized upon inhibition of HSP90 and are thus likely clients of this chaperone, but it is unclear whether these proteins first bind HSP90 and are then transferred to the R2TP, or whether they first become associated to the R2TP, which would then recruit HSP90 to these clients. HSP90 cofactors are divided in early and late co-chaperones, depending on whether they help to load or unload clients on the chaperone. This often correlates with how the co-chaperone affects HSP90 ATPase activity. Early co-chaperones inhibit ATPase activity to maintain an open HSP90 structure compatible with client loading, while late co-chaperone stimulates HSP90 ATPase activity to promote release of the clients.[91] In this regard, the status of the R2TP complex is not entirely clear as RPAP3 has been reported to both inhibit and stimulate HSP90 ATPase activity, depending on its association with PIH1D1. A possibility would be that it both helps to transfer clients from HSP70 to HSP90, and then to load the folded client to downstream complexes.[69,92,93]

PIH1D1 has been proposed to function as an adaptor between client proteins and the R2TP complex,[94,95] and for a review see.[81] This seems to be mediated by the PIH1D1 N-terminal domain that was described as a phospho-peptide binding domain recognizing a DSDD/E motif in which the serine is phosphorylated.[94,96] Interestingly, yeast NOP58 has such a motif (443DS(p)DDE447) and although it does not seem absolutely required to mediate interactions with the R2TP, it may reinforce this association.[77,95,97] In higher eukaryotes, NOP58 lacks the DSDD motif. These organisms however have the C12orf45 factor, which tighly associates with NOP58 and may mediate its interaction with the R2TP.[84] Thus, the details of interactions might differ substantially between yeast and human systems, in agreement with rather important differences between the homologs of PIH1D1 and RPAP3. The yeast RPAP3 is a small protein that functions as an adaptor between HSP90 and yeast PIH1D1, while human RPAP3 is a much larger protein that has likely gained additional functions.[93]

The interaction of SNU13 with the R2TP complex appears to be mediated by NUFIP, since NUFIP interacts with both SNU13 and PIH1D1 in human and yeast, and can also bridge the 2 proteins together.[68,97] It is however possible that, as in the case of NOP58, additional interactions occur to facilitate the assembly process.

The assembly of box H/ACA RNPs

Two conserved proteins are specifically required for the assembly of box H/ACA RNPs, NAF1 and SHQ1. They have been first identified in yeast, as yeast DKC1 interacting proteins, and are required for the stability of box H/ACA RNAs without being part of the mature particles.[22,98-103] These 2 factors are nucleocytoplasmic shuttling proteins that localize to the nucleoplasm and are excluded from the nucleoli and CBs.[22,98-100,102,104]

NAF1 drives co-transcriptional assembly and controls the activity of immature box H/ACA snoRNPs

While biogenesis of box C/D RNP assembly is generally linked to splicing, assembly of mammalian and yeast box H/ACA RNPs is believed to occur on the nascent pre-mRNA in a splicing independent manner (Fig. 3).[22,99,105-107] Accordingly, binding of box H/ACA core proteins is independent from selection of pre-mRNA splice sites, but is connected to RNA polymerase II transcription.[107] This connection is performed by NAF1, which interacts with the C-terminal domain (CTD) of the large subunit of RNA polymerase II, and which may recruit H/ACA core proteins to the newly synthesized box H/ACA RNAs.[22,99] GAR1 is however not found at the H/ACA transcription site with the other core proteins, but is concentrated within nucleoli and CBs, where mature box H/ACA RNPs reside.[22] This protein may associate later in the maturation process, via a remodeling event that would exchange NAF1 for GAR1. Structural studies show that a domain of NAF1 is structurally similar to the core domain of GAR1, which interacts with DKC1.[108] In agreement, NAF1 and GAR1 bind to DKC1 in a mutually exclusive manner.[22,55] NAF1-containing pre-snoRNPs are inactive and the replacement of NAF1 by GAR1 allows the formation of an active enzyme.[22,62] The mechanism leading to the replacement of NAF1 by GAR1 is still unknown. Using yeast proteins, it was shown that the domain of yeast NAF1 that binds yeast DKC1 also mediates yeast NAF1 dimerization.[62] Therefore, the yeast NAF1 dimer shows little affinity for yeast DKC1 and modulation of the dimeric state of yeast NAF1 may regulate the formation of mature box H/ACA snoRNP.[62] In mammalian cells, the SMN complex has also been proposed to play a role in the exchange between GAR1 and NAF1. The SMN complex is highly concentrated in the CBs where the exchange is proposed to occur, and the SMN protein has been shown to interact directly with GAR1.[22,109,110] Decreased level

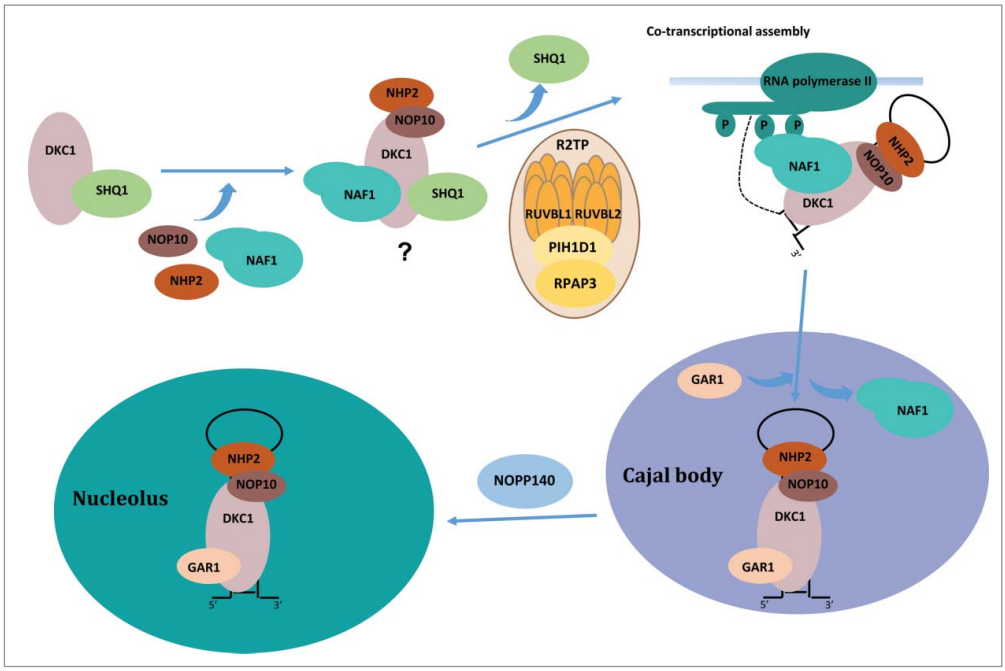

Figure 3. Assembly and trafficking of box H/ACA RNPs. The first step of box H/ACA RNP assembly is the interaction of SHQ1 with DKC1 to prevent its illicit binding to non-specific RNAs. SHQ1 is released with the help of the R2TP complex, allowing the interaction of DKC1 to nascent H/ACA RNAs at their site of transcription. At this step, NHP2 and NOP10 are present in the pre-particle, as well as another assembly factor NAF1 that interacts with the CTD of RNA polymerase II and keeps the H/ACA RNP inactive. Finally NAF1 is replaced by GAR1 to produce mature and functional H/ACA RNPs. ScaRNPs are retained in the CBs, whereas box H/ACA snoRNPs are transported to the nucleoli.

of RNA pseudouridylations and increased association of the pre-snoRNAs with NAF1 occur in mammalian cells depleted of both UNRIP (one component of the SMN complex) and NOPP140 (a snoRNP transport factor, see below), reinforcing a possible role for the SMN complex in box H/ACA RNP assembly.[111]

SHQ1 is a chaperone for DKC1

SHQ1 interacts with DKC1 in the absence of the other H/ACA proteins or snoRNAs, and it is not present at the site of snoRNA transcription, indicating that it acts at an early step of box H/ACA biogenesis.[102,106] The cellular location where the SHQ1/DKC1 complex is formed is not clear. However, since DKC1 alone is not stable, it was proposed to interact with SHQ1 in the cytoplasm as soon as it is synthesized, thereby protecting it from aggregation and degradation.[102] SHQ1 contains 2 well-defined conserved domains, a CHORD and Sgt1 domain (CS) and a C-terminal Shq1-specific domain (SSD). The CS domain of SHQ1, in contrast to the CS domain found in authentic HSP90 co-chaperones, fails to interact with HSP90.[103,112] However, it is possible that SHQ1 interacts with HSP90 only in a defined conformation or when it is bound to another yet unknown factor. Both domains of SHQ1 make contact with DKC1, forming a tight clamp around the protein.[70,102,103,112-115] Moreover, the SSD domain functions as a RNA mimic, docking to the RNA binding surface of DKC1.[113,114] This likely prevents illicit binding to RNAs.

A speculative model for the assembly of H/ACA snoRNPs

The available *in vivo* and *in vitro* data suggest a model for the assembly of box H/ACA snoRNPs (Fig. 3). Rapidly after its synthesis, DKC1 would associate with SHQ1. The other proteins would then be recruited to the pre-particles, and several possibilities exist. First, NAF1, NHP2, NOP10 may associate with the SHQ1/DKC1 complex. An RNA-free complex containing SHQ1, NAF1, NHP2, NOP10 and DKC1 can be indeed assembled using recombinant yeast proteins, supporting this hypothesis.[114] However, a nuclear tethering assay in U2OS cells and *in vitro* experiments with the rat proteins showed that binding of SHQ1 to DKC1 excludes recruitment of NOP10, NHP2, and NAF1.[102] Thus, SHQ1 may also be released from DKC1 before or concomitantly to the recruitment of these proteins. In any case, following assembly of a protein-only complex, NAF1 would help to recruit this complex to nascent H/ACA RNAs, and binding of DKC1 to the RNA would definitively exclude SHQ1 from pre-snoRNPs. The nascent snoRNP complex would then be routed to CBs, where NAF1 would be exchanged for GAR1.

Role of the HSP90/R2TP system in snoRNP assembly

Although a large number of interactions and functional data have shown the importance of the HSP90/R2TP system in the assembly of both box C/D and H/ACA snoRNPs, the exact molecular function of this complex is still not well understood. The key players appear to be HSP90 itself and the RUVBL1/2 ATPases, while PIH1D1 and RPAP3 most likely function as adaptors and regulators of these enzymes. HSP90 is required to stabilize NOP58 and SNU13 before and/or during the assembly, and its well-known chaperone function suggests that it may help to keep these proteins into a conformation compatible for assembly. By contrast, the function of the RUVBL1/2 ATPases is much more elusive. They are known to make ATP-dependent contacts with a number of core proteins and

assembly factors, and structural studies have shown that ATP induces conformational changes in the ring formed by the hetero-hexamer formed by these proteins.[116] ATP binding and hydrolysis/release may thus function to trigger maturation of pre-snoRNP complexes. On one hand, RUVBL1/2 may stabilize assembly intermediates such as the protein-only complex of pre-snoRNPs. On the other hand, these ATPases may dissociate assembly factors from core proteins to promote maturation. This last possibility has received a solid support from the study of H/ACA snoRNPs, where it was shown that RUVBL1/2 are required to dissociate SHQ1 from DKC1.[70] Recruitment of the R2TP complex to H/ACA snoRNPs may occur via an interaction of NUFIP with NHP2,[68] via the binding of RUVBL1/2 to DKC1 and SHQ1, via the binding of PIH1D1 to DKC1,[70] or via additional uncharacterized interactions.

Trafficking of box C/D and H/ACA snoRNPs during their biogenesis

Box C/D and H/ACA snoRNAs are synthesized in the nucleoplasm and they have to be transported to the nucleolus. The maturation of snoRNPs occurs entirely in the nucleus,[39,117] and this contrasts with spliceosomal snRNAs, which have a transient cytoplasmic phase during their maturation.[118,119] Studies analyzing snoRNP trafficking have shown that the conserved box C/D and H/ACA motifs are necessary and sufficient for nucleolar localization.[31,120-124] In higher eukaryotes, snoRNAs are first transported to CBs before being routed to nucleoli.[31,121,125] Factors and processes that facilitate these orderly localization events have been partially characterized.

Transport of snoRNAs to Cajal bodies

Trafficking of box C/D snoRNAs was analyzed using few model RNAs, and in particular U3, a box C/D snoRNA that is independently transcribed from its own promoter. As the other independently transcribed snoRNAs, U3 is synthesized as an m^7G-capped precursor that carries a 3′-extension, and its cap is matured in the nucleus by the hypermethylase TGS1 to generate the final, TMG-capped snoRNA. U3 precursors form a large, structurally dynamic complex with numerous non-snoRNP proteins.[68,90,126,127] This complex contains factors involved in transport (CBC, PHAX, NOPP140, CRM1 and Ran), RNP assembly (NUFIP, the R2TP and HSP90) and RNA processing (TGS1, ARS2, La, LSm proteins and components of the RNA exosome), for a review see ref.[19] Surprisingly, many of these proteins also bind the m^7G-capped precursors of snRNAs (e.g. CBC, PHAX, ARS2, CRM1, TGS1), although these precursors follow a distinct maturation that involves their export to the cytoplasm. Furthermore, these proteins are linked to the cap and have different roles in snRNA and snoRNA trafficking. On one hand, nuclear export of m^7G-capped snRNA precursors relies on an export complex formed by the CBC, the CBC-binding proteins ARS2 and PHAX, and the exportin CRM1 that is recruited by PHAX,[127] and reviewed in.[118,119] On the other hand, m^7G-capped precursors of U3 are routed to CBs,[128] and these precursors appeared to be routed to CBs in a CBC and PHAX-dependent manner and in a CRM1-independent manner.[126] Mutation of the conserved C/D boxes triggers export of m^7G-capped U3 precursors, indicating that assembly of the snoRNP is essential to re-direct the transport function of PHAX toward CBs. The molecular details of these sorting events are however unknown. Another unsolved issue deals with the trafficking of intronic snoRNAs, as these RNAs do not have a cap but are nevertheless routed toward CBs. It is possible that PHAX could have a role in this process, but binding of PHAX to intronic snoRNAs has not yet been reported.

The transport of snoRNAs from Cajal bodies to nucleoli reveals a nuclear role for CRM1

Heterokaryon assays have clearly demonstrated that snoRNAs do not transit through the cytoplasm during their biogenesis[39] while U8 snoRNA may be an exception.[129] Nevertheless, transport of U3 from CBs to nucleoli has surprising requirements for CRM1 and for functional nuclear pores.[39,126] This conundrum was recently solved by showing that CRM1 controls the composition of pre-snoRNP complexes, and in particular their association with TGS1, the snRNA/snoRNA cap hypermethylase. In vertebrates, TGS1 is produced in 2 isoforms, a long isoform (TGS1-LF) and a short isoform (TGS1-SF) that is produced by the degradation of the N-terminus of the long isoform by the proteasome.[130] TGS1-LF contains an NES, it localizes to both the cytoplasm and CBs, and is involved in snRNA cap-hypermethylation. The short isoform localizes only to CBs and modifies the cap of snoRNAs. Consistently, the long and short isoform differentially interact with snRNA and snoRNA precursors. The N-terminus specific to TGS1-LF contains a binding site for the C-terminal extension of SmB, a core protein of snRNAs, while the C-terminal region present on both the short and long isoform of TGS1 contains the methylase activity, as well as a binding site for the highly charged C-terminal extensions of NOP56/NOP58 and DKC1. Interestingly, these extensions function as nucleolar localization signals (NoLS) for snoRNPs, and the binding of the long form of TGS1 was proposed to mask these NoLSs.[39] *In vitro*, the binding of CRM1 to TGS1-LF displaces it from snoRNP NoLS. Thus, when CRM1 is inhibited by Leptomycin B treatment, TGS1-LF accumulates in the nucleus, binds the snoRNP NoLS and prevents their nucleolar localization. In contrast, when CRM1 is not inhibited, it dissociates TGS1-LF from the snoRNP NoLS, thereby promoting nucleolar transport of snoRNPs and export of TGS1-LF to the cytoplasm. The role of CRM1 in the transport of snoRNPs to the nucleolus is thus linked to the binding of CRM1 to TGS1-LF.[39]

Like U3, intronic box C/D snoRNAs require CRM1 and functional pores to reach nucleoli. In addition, microarray analyses have shown that TGS1-LF binds intronic C/D and H/ACA snoRNAs, as well as the telomerase RNA, and that this binding is promoted by the inactivation of CRM1. Thus a similar mechanism may operate to release these RNAs from CBs.[39,126] These studies indicate that CRM1 plays a nucleoplasmic role in snoRNP trafficking, which is to modify the composition of pre-snoRNP complexes to license them for nucleolar transport.[39]

Additional factors involved in the transport of snoRNPs to nucleoli

NOPP140 is a nucleocytoplasmic shuttling phospho-protein mainly detected in nucleoli, but also present in CBs.[131,132] NOPP140 interacts with both box C/D and H/ACA snoRNPs

and expression of a dominant negative mutant of this protein depletes snoRNPs from nucleoli and CBs.[22,90,132-135] Since NOPP140 shuttles between the nucleolus and the CBs, it has been suggested that it functions in the intranuclear transport of snoRNPs between the 2 organelles.[133,134]

Within nucleoli, snoRNPs accumulate in the dense fibrillar compartment (DFC) where early processing of the rRNA takes place.[136] In yeast, inactivation of the homolog of the nucleolin gene depletes snoRNPs from the DFC, and they accumulate in another nucleolar compartment. Nucleolin directly binds pre-rRNAs and snoRNPs, and could thus facilitate interactions of snoRNPs with pre-rRNAs. Processing of pre-rRNAs is very rapid in yeast,[137] and these interactions may help these rapid kinetics.

Function of Cajal bodies in snoRNP biogenesis

M^7G-capped, 3′-extended precursors of U3 accumulate in CBs together with TGS1, indicating that they are likely hypermethylated there.[128] Intronic snoRNAs do not carry a cap, but CBs might also play a role in the maturation of these RNAs. For instance, FBL and GAR1 have also been suggested to become stably associated to snoRNPs in this compartment.[22,90,128] These proteins interact with SMN and this process may thus be facilitated by the SMN complex,[109,110,138] whose localization in CBs depends on its interaction with coilin.[139] Spliceosomal snRNAs are base-modified in CBs by scaRNAs, and it is thus also possible that some snoRNAs are modified there. Finally, the accumulation of snoRNAs and snRNAs in CBs has been proposed to enhance RNP biogenesis by favoring interactions between partners.[140,141] This function is carried out by coilin, which directly interacts with many CB proteins as well as numerous non-coding RNAs, including snoRNAs and scaRNAs.[125,142,143] Coilin may promote RNP biogenesis in the CBs by acting as a chaperone of small non-coding RNAs, by interacting with both proteins and RNAs and increasing their local concentration, thereby favoring their interactions. It should be however kept in mind that transit of snoRNAs and snRNAs to CBs may not be absolutely required for their biogenesis as several cell types do not have detectable CBs and nevertheless, non-coding RNPs are correctly produced in these cells. It is possible that all the reactions normally occurring in CBs can also take place between individual molecules freely diffusing in the nucleoplasm. Alternatively, it is possible that RNP maturation would occur in "nano-CBs," which would be too small to be detected by traditional microscopy techniques. Interestingly, over-expressing some non-coding RNAs can trigger the appearance of CBs in cells that lack them. It is thus possible that the size of CBs adapts to the incoming flux of incompletely assembled RNPs, and that they enlarge when some steps in RNA biogenesis linked to CBs become limiting.

CBs have been described in high eukaryotes and their formation is believed to result from self-assembly properties of their components.[144,145] In the yeast *S. cerevisiae*, it appears that components mediating snoRNP biogenesis like TGS1 have some ability to self-assemble and to form a sub-nucleolar structure that was named the Nucleolar Body (NB).[21] As for CBs, precursors of snoRNAs can be detected in NBs and it was proposed that NBs could be the site of snoRNP assembly and processing.[128] Genes coding for the homologous proteins of coilin and SMN have not been identified in *S. cerevisiae* but human SMN, when expressed ectopically, localizes to NBs.[21] It thus appears that the compartmentalization of snoRNA biogenesis can occur even in absence of canonical CBs.

Localization of scaRNPs in Cajal bodies

Box H/ACA scaRNAs carry a universally conserved CB localization signal sequence with an ugAG consensus sequence, called the CAB box. This box is located in the terminal loop of the 5′ and/or 3′ hairpins of the RNAs, and is necessary for localization to CBs.[16,146] Human telomerase RNA also localizes to CBs in a CAB box- and cell cycle- dependent manner.[16,17,147,148] Failure of the telomerase RNA to transit through the CBs or disruption of the CBs induce defects in telomerase recruitment to telomeres and in telomere extension.[149-152] Mutations of the CAB box result in the appearance of the scaRNAs in the nucleoli, and addition of CAB box motifs targets authentic snoRNAs into CBs, indicating that the CAB signal functions as a CB retention motif.[146] This motif is required for the binding of the WD-repeat protein 79 (WDR79, or TCAB1/WRAP53).[149,153] This protein is essential for CB maintenance.[154] It is associated with the 2 major components of CBs, SMN and coilin, and is believed to recruit the SMN complex to CBs by mediating interactions between SMN, importin β and coilin.[143,154] ScaRNP localization to CBs also requires the ACA box, suggesting that WDR79 interaction to box H/ACA scaRNPs requires assembly of the core proteins.[146,149,153]

A CAB-like motif (consensus cgaGUUanUg) is present in *D. melanogaster* Box C/D scaRNAs and the fly homolog of WDR79 interacts to this sequence.[153] In human, the CAB motifs of the scaRNAs containing both box C/D and H/ACA domains are required for their localization to CBs.[146] It was shown recently that a (GU)-rich terminal stem-loop represents the cis-acting CB localization element bound by WDR79 in vertebrate intron-encoded box C/D scaRNAs.[153,155] It should also be mentioned that AluACA RNAs also associate with WDR79 although they accumulate in the nucleoplasm rather than in CBs.[18]

Conclusion

Eukaryotic snoRNP assembly is a complex process in which the HSP90/R2TP chaperone system plays an important role. So far, only archeal snoRNPs can be assembled *in vitro* into active particles. In eukaryotic cells, some core proteins of snoRNPs are likely clients of HSP90 and the R2TP complex plays a role together with assembly factors to build a protein-only pre-snoRNP complex that further allows the formation of a mature snoRNP. The role of these machineries would be to chaperone unassembled core proteins, regulate the formation/disassembly of assembly intermediates, transport core proteins to the site of assembly in the nucleus, prevent inaccurate formation of RNP complexes, and control the catalytic activity of pre-snoRNPs. Future structure/function studies of these assembly machines should lead to a detailed picture of box C/D and box H/ACA snoRNP biosynthesis.

Mature snoRNPs are involved in rRNA maturation and they reside in the nucleolus, whereas box C/D and box H/ACA scaRNPs direct spliceosomal snRNA modification and reside in CBs. Sequestration of functionally active RNPs either in nucleoli or CBs may be an important mechanism to avoid undesired RNA modification events in the nucleoplasm. CBs are the sites for the maturation of nucleolar snoRNPs and these RNPs have to be further transported to nucleoli. This is not the case for scaRNPs which are retained in CBs by a mechanism involving WDR79. Future studies will be needed to clearly understand the mechanisms that tightly regulate trafficking of all these different families of RNPs.

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