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REVIEW

Cajal bodies and snRNPs - friends with benefits

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ABSTRACT

Spliceosomal snRNPs are complex particles that proceed through a fascinating maturation pathway. Several steps of this pathway are closely linked to nuclear non-membrane structures called Cajal bodies. In this review, I summarize the last 20 y of research in this field. I primarily focus on snRNP biogenesis, specifically on the steps that involve Cajal bodies. I also evaluate the contribution of the Cajal body in snRNP quality control and discuss the role of snRNPs in Cajal body formation.

Biogenesis of snRNPs

Spliceosomal small nuclear ribonucleoprotein particles (snRNPs) are complex particles that consist of small (< 200 nt) nuclear RNA (snRNA), a heptameric ring of Sm or Like-Sm (LSm) proteins and 1 to 12 proteins that are specific for each snRNP. There have been 5 major and 4 minor snRNPs that have been described, each named according to the snRNA that they contain. The major snRNPs are U1, U2, U4, U5 and U6 and the minor snRNPs have been designated U11, U12, U4atac and U6atac. It is of note that the U5 snRNP is common to both major and minor splicing pathways.

All snRNPs proceed through an interesting assembly pathway that involves several cellular compartments. Spliceosomal snRNPs follow a general rule, which states that composite particle maturation occurs primarily in compartments, which differ from the final destination of the mature particle. Biogenesis of snRNPs has been covered by several comprehensive reviews.[1-6] In this review, I will specifically focus on the role of Cajal bodies (CBs) in snRNP maturation and the emerging function of CBs in quality control of the assembly process.

With the exception of U6 and U6atac, all snRNAs are transcribed by RNA polymerase II, however they are not polyadenylated. Their 3′ end processing is closely coupled to transcription and depends on the 3′ box located 9–19 nt downstream of the mature 3′ end.[7] The first processing step involves endonucleolytic cleavage upstream of the 3′ box, which leaves a tail of a couple nucleotides that requires further trimming. The Integrator complex, first isolated and described by Ramin Shiekhattar and colleagues was shown to play an essential role in initial 3′ end processing.[8] 3′ end cleavage is coupled to proper transcription termination via the cap-binding complex and SRRT (ARS2).[9,10] After transcription and initial 3′ end processing, partially processed snRNAs are exported to the cytoplasm in a m7G-cap dependent manner. Export is facilitated by the exportin XPO1 (CRM1), RanGTP as well as the adaptor proteins NCBP20 (CBP20) /NCBP1 (CBP80), PHAX and SRRT.[9,11] In

addition, NONO and SFPQ (PSF) promote the association of PHAX with snRNAs.[12] In the cytoplasm, a heptameric ring of 7 Sm proteins is assembled around the consensus Sm-binding sequence (AUUUUUG), resulting in the formation of the core snRNP. Assembly of the Sm ring is promoted and controlled by PRMT5 and SMN complexes (reviewed in[2] and ref. therein). After Sm ring formation, the m7G-cap is hypermethylated by TGS1 followed by the final 3′ end trimming.[13-15] However, localization of the final trimming step has not been clearly resolved. Studies preformed in human cell culture have shown that the trimming activity resides in the cytoplasm,[13,16] while results in *Xenopus leavis* oocyte placed final snRNA trimming in the nucleus after import from the cytoplasm.[17] The trimethylguanosine cap, together with the Sm-ring, serve as signals for nuclear import. The trimethylguanosine dependent import pathway has been well described and involves the protein Snurportin-1, which binds the trimethylguanosine cap and acts as a bridge between the trimethylguanosine cap and importin-β.[18-20] Although the exact molecular mechanism of the pathway dependent on Sm proteins has yet to be revealed, it has been determined that the SMN complex interacts in the cytoplasm with the core snRNP and importin-β which lead to the proposal that the SMN complex is involved in snRNP nuclear import.[21,22] In addition, Importin 7 was shown to participate in the snRNP import pathway in *Drosophila melanogaster*.[23] After re-import, several snRNA nucleotides are modified by scaRNA-directed methylation and pseudouridylation.[24]

In regards to the final steps of snRNP biogenesis and the addition of snRNP-specific proteins, available information is rather sparse. However, several findings indicate that the addition of snRNP-specific proteins occurs after import of the core snRNP into the cell nucleus. Both U1 and U2 snRNP-specific proteins have been shown to be imported into the nucleus independently of snRNAs.[25-27] Similarly, U4 and U5 snRNAs reach the nucleus after the depletion of key snRNP-specific proteins Prpf8 and Prpf31.[28,29] Together, these findings

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imply that snRNP-specific proteins are added after the core snRNP has entered the nucleus. Injection of fluorescently labeled U4 and U5 snRNAs into the *Xenopus laevis* oocyte revealed the occurrence of transient nucleolar localization.[30] However, nucleolar localization has not been observed in human cells (our unpublished data and[31]).

Several chaperones have been shown to assist in the addition of snRNP-specific proteins to the core snRNP. In yeast, Aar2p interacts with Prp8p before the addition of other U5-specific proteins promoting U5 snRNP formation.[32] Structural studies have revealed a mutually exclusive binding of Prp8p protein with Aar2p and Brr2p.[33,34] The Prp8p-Aar2p interaction is disrupted upon Aar2p phosphorylation which represents the molecular switch between Aar2p and Brr2p binding to Prp8p.[33] In *Drosophila melanogaster*, the ECD protein interacts with U5 snRNP proteins and likely participates in U5 snRNP assembly.[35] Finally, NUFIP and the HSP90/R2TP chaperone system were found to interact with U4-specific Prpf31 and assist with U4 snRNP biogenesis.[28] Less is known about chaperons involved in U1 and U2 snRNP assembly. U1-specific SNRNP70 (U1-70K) has been recently found to interact with the SMN complex and promote Sm ring assembly specifically on the U1 snRNA,[36,37] which suggests that SNRNP70 interacts with U1 snRNA in the cytoplasm. Both U1 snRNA and SNRNP70 have been detected in gems, nuclear structures that are rich in SMN complexes.[36] SNRNP70 interacts with the SMN complex also in the cell nucleus suggesting that nuclear SMN is involved in U1 snRNP maturation and/or recycling.[36,38] Alternatively, nuclear SNRNP70-SMN complexes could represent post-imported U1 particles. U2 snRNP biogenesis proceed through 3 distinct complexes: the 12S complex, the 15S complex and 17S complex. These complexes reflect addition of SNRNPA1 (U2A) and SNRPB2 (U2B") proteins, the SF3b complex, and the SF3a trimeric complex, respectivelly.[39] 17S U2 snRNP associates with additional proteins including Tudor domain containing SMNDC1 (SPF30), DEAH-box helicases DHX15 (hPrp43) and DDX46 (hPrp5) and the U2AF dimer.[40]

The U6 snRNP follows a different biogenesis pathway. U6 snRNA is synthesized by RNA polymerase III and remains in the cell nucleus. New U6 transcripts contain an extended tail of uridines, which are added by the TUTase TUT1.[41,42] Like other RNA polymerase III transcripts, the U-stretch at the 3′ end of the U6 snRNA is bound by the La protein that protects RNAs from degradation and facilitates their further maturation.[43] The mature U6 snRNA associates with a ring of 7 LSm 2–8 proteins. The LSm2-8 ring is pre-assembled without RNA in the cytoplasm and is localized to the nucleus by the LSm8 protein.[44,45] The 5′ end of U6 contains a γ-monomethyl cap while the 3′ end ribose is protected by cyclic 2′-3′ phosphate which is formed by USB1, a protein that is mutated in patients with the rare hereditary disease, Clericuzio-type poikiloderma with neutropenia.[46] The formation of the cyclic phosphate at the 3′ end destabilizes La binding and facilitates LSm2-8 association with the U6 snRNA.[47] U6 snRNA is also modified by methylation as well as the isomerization of uridines to pseudouridines, but these modifications are guided by snoRNAs and occur in the nucleolus.[48,49] The key role of the nucleolus in U6 biogenesis has been further documented by following the path of microinjected U6 snRNA through the nucleolus and nucleolar localization of TUT1.[42,50] U6 snRNA further interacts with SART3, which targets U6 snRNA to CBs and promotes U4/U6 annealing.[51-53] A new U6 snRNA modifying TUTase USIP-1 has been recently identified in *Caenorhabditis elegans*. This enzyme interacts with an LSm-free U6 snRNP containing SART3, which lead to the speculation that USIP-1 specifically associates and modifies the U6 snRNA released after splicing.[54]

The completion of snRNP biogenesis is finalized with the formation of the composite particles, U4/U6 and U4/U6•U5. First, U4 and U6 snRNAs are brought together by the combined action of SART3 and LSm 2–8 proteins.[53,55] After U4/U6 duplex formation, U4/U6 specific proteins are added creating the U4/U6 particle.[56] The U4/U6 snRNP further associates with the U5 snRNP to form the mature U4/U6•U5 tri-snRNP. The interaction between U4-specific Prpf31 and U5-specific Prpf6 is essential for tri-snRNP assembly,[57,58] however, other snRNP proteins, namely Prpf3 and EFTUD2 (hSnu114), participate and secure tri-snRNP stability as well.[59,60] Structural studies of yeast and human tri-snRNPs revealed a beautiful arch that consists of EFTUD2 TPR repeats and connects U5 and U4 proteins.[61,62] The structure of the human tri-snRNP also points to the important role of USP39 (Sad1, U4/U6•U5-65kD subunit) in sealing the tri-snRNP structure.[62] Finally, the splicing competent U4/U6•U5 snRNP is assembled and ready for splicing.

There is less known about the biogenesis of minor snRNPs. U4atac/U6atac snRNP contains the same set of proteins as the U4/U6 snRNP and likely follows the same maturation pathway as its major counterparts. U11 and U12 snRNPs enter the splicing reaction as a pre-assembled complex with the assistance of 2 important proteins that contribute to U11/U12 snRNP formation, RNPC3 (U11/U12-65K) and PDCD7 (U11-59K).[63]

Cajal bodies and snRNPs - a close relationship

CB is closely linked to spliceosomal snRNAs and snRNPs. Shortly after the discovery of coilin, a marker and scaffolding protein of CBs (reviewed in[64]), snRNAs were detected in these nuclear compartments.[65,66] Since this important finding, the debate regarding the function of CBs in snRNA/snRNP metabolism has been ongoing. Soon afterwards, the hypothesis that splicing takes place in CBs was neglected. It has since become clear that CBs are involved in many aspects of short non-coding RNA metabolism including snRNP biogenesis, but we still lack a comprehensive and detailed understanding of the exact role of CBs in this process. The importance of coilin has been shown in several studies including the reduction of litter size in coilin knockout mice suggesting problems with embryogenesis and/or fertility.[67,68] Similarly, coilin depletion in fish embryos has been shown to be lethal.[69] Flies without coilin are fully viable and fertile[70] but have problems with egg-laying regulation (Joe Gall, personal communication). Similarly, plants are also viable without coilin, however coilin mutations, which disrupted CBs, showed changes in the expression pattern of a subset of genes.[71,72] It should be noted that changes in mRNA expression were also observed after disruption of CBs in human cell culture.[73] Despite significant progress, we are still

far from complete understanding of CB molecular function. In the text that follows, readers can find an up-to-date description of our current knowledge of the role of CB in snRNA and snRNP.

Pre-export events: snRNA transcription and 3′ end processing

Both major and minor U snRNA genes are often found in the vicinity of nuclear CBs.[73-76] Several studies have provided evidence that snRNA transcription and nascent snRNAs are necessary for the association of CBs with U snRNA gene.[77-80] It was recently suggested that CBs are involved in the organization of snRNA genes within the nuclear space.[73] The tight connection between CBs and snRNA genes was further demonstrated by Karla Neugebauer and colleagues. They used unbiased chromatin immunoprecipitation followed by DNA-seq to show the association between coilin and snRNA genes.[81] CBs are thus connected to snRNAs from their birth and knockdown of proteins that are essential for CB integrity (WRAP53 and USPL1), result in lower expression of all snRNAs.[73] How exactly CBs enhance snRNA expression is currently unclear. However, CBs could directly regulate snRNA transcription via a regulatory feedback mechanism where they "sense" the amount of total snRNAs and regulate snRNA transcription of nearby snRNA genes accordingly.[82]

The U2 pre-snRNA is highly concentrated in CBs, which points to the role of CBs in snRNA 3′ end processing.[83] In addition, Int4 and Int11 subunits of the Integrator complex are important for CB integrity, which further supports a connection between Integrator and CBs.[84] The Int4 subunit was localized to CBs,[84] however other Integrator subunits do not specifically accumulate in CBs.[85] Considering that coilin

directly associates with snRNAs and might even have a direct role in their processing,[81,86] it is feasible to conclude that CBs are involved in 3′ end processing of pre-snRNAs. However, the exact role and the importance of CBs in this process have yet to be clarified.

After 3′ end cleavage, snRNAs are exported to the cytoplasm by a complex, which contains, among other proteins, XPO1 and PHAX, which are both located in CBs.[78,87,88] In addition, inhibition of PHAX results in the accumulation of U1 snRNA in *Xenopus laevis* oocyte CBs.[89] These findings together suggest that newly transcribed snRNAs pass through the CBs on their way out of the nucleus supporting the idea that the export complex is assembled in CBs (Fig. 1).

Post-import events: snRNA modification, snRNP assembly and recycling

After completing the cytoplasmic phase, the core snRNPs (snRNAs+Sm proteins) return to the nucleus and first accumulate in CBs.[90] However, the precise molecular signals that navigate core snRNPs to CBs are unknown. Coilin interacts directly with snRNAs and the Sm proteins, thus both possibly serving as a CB targeting signals.[81,91] It was recently shown that SART3 is important for proper CB localization of U4 and U5 snRNAs but the molecular mechanism has been elusive.[29] Also the SMN complex, which interacts with the Sm ring in the cytoplasm, was suggested to target new snRNPs to CBs through the interaction of the SMN Tudor domain with the coilin RG-box.[21,22,88,92] However, the key experiments that would identify the CB targeting signal have yet to be performed.

After import to the CB, new snRNA is modified by 2′-O-ribose methylation and by isomerization of uridines to
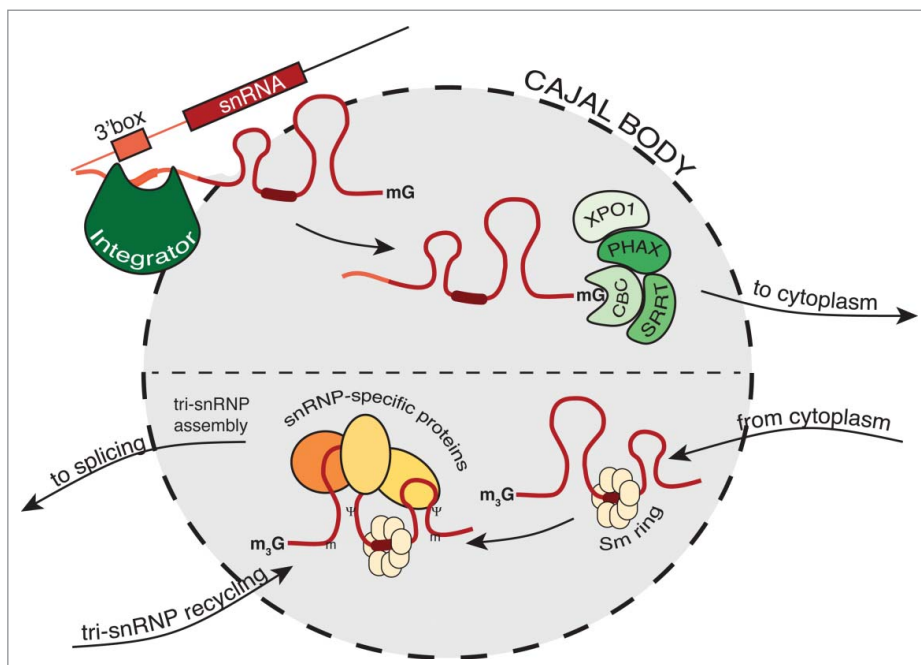
Figure 1. Cajal body is involved in different steps of snRNP biogenesis. First, the Integrator cleaves the 3′ end of snRNA. Then, the export complex forms at the 5′ end and snRNA is exported to the cytoplasm. After Sm ring assembly and cap hypermethylation, the core snRNP returns to the Cajal body where snRNP-specific proteins are added and U4/U6•U5 tri-snRNP forms.

pseudouridines. Modified nucleotides are selected by short non-coding RNAs - scaRNAs which are specifically localized in CBs.[93] In *Drosophila melanogaster*, scaRNAs are also localized in CBs but a coilin null mutant lacking CBs exhibited normal levels of snRNA methylation and pseudouridylation.[94] These results indicate that post-transcriptional modification of snRNAs primarily occurs in CBs but these structures are not essential, at least in flies.

Core snRNPs must further associate with snRNP-specific proteins. When this process is inhibited, snRNAs accumulate in CBs, which strongly suggests that core snRNPs meet their specific protein partners primarily here.[28,29] The final step in snRNP maturation is the formation of the splicing competent U2 and U4/U6●U5 snRNPs. U2 snRNP maturation, specifically the formation of the 17S complex, has been shown to occur in CBs.[27,95] Also U4/U6 and U4/U6●U5 snRNP assembly has been placed in CBs.[51,52,57]

During splicing, the tri-snRNP undergoes a remarkable rearrangement, which results in the release of individual snRNPs from the post-splicing spliceosome. However, the exact molecular composition of snRNPs after splicing is not well defined. The U6 protein, SART3, is released well ahead of splicing during tri-snRNP assembly.[53] U6-specific LSm proteins are destabilized during splicing,[96] which suggests that U6 snRNA is released as naked snRNA! U4/U6 snRNP-specific proteins leave the spliceosome at the same time as U4 snRNA although it is not known whether these proteins remain bound to the U4 snRNA. However, it is reasonable to speculate that SNU13, which directly binds the U4 kink-turn motif,[97] stays stably associated with the released U4 snRNA. Also Prpf31, which is bound to the SNU13-U4 snRNA complex, remains likely linked to the released U4 snRNP.[98] The only molecularly characterized post-splicing snRNP is the 35S U5 snRNP, which contains 4 of the 6 U5-specific proteins, proteins from the NTC complex and step 2 factors.[99] Little is known about the factors that recycle the post-splicing snRNP and reassemble functional snRNPs. SART3, a protein that is highly accumulated in CBs,[52] was shown to act in U4/U6 reannealing.[53] Because snRNPs repeatedly cycle through CBs and U4/U6 snRNPs accumulate in CBs after inhibition of spliceosome recycling it is reasonable to speculate that CB are involved in snRNP re-assembly after splicing.[100]

There is virtually no information available that addresses the stability of snRNPs *in vivo* or the requirements to repair the Sm-ring and/or snRNP-specific proteins. The SMN complex has been also found in the nucleus (gems and CBs) and has been suggested to be important for snRNP recycling.[101] Thus, it is plausible that the nuclear SMN complex is involved in the repair of damaged Sm rings, which might take place in CBs. An alternative hypothesis suggests that the SMN complex disassembles the Sm ring during snRNP degradation.

Quality control in Cajal bodies

The quality of snRNP formation is apparently controlled at several checkpoints along the assembly pathway (Fig. 2). First, it has been suggested that the exosome, TRAMP and the NEXT complex are involved in recognition and degradation of aberrant snRNAs in the nucleus but a molecular mechanism that describes how misfolded snRNAs are

recognized is unknown.[102,103] Furthermore, it has been shown that inhibition of the snRNP export complex formation leads to the accumulation of snRNAs in CBs of the *Xenopus laevis* oocyte, which suggests the existence of a quality control checkpoint, which monitors snRNA before their export from the nucleus.[89] In the cytoplasm, U1 snRNAs, which lack the functional Sm-binding sequence are degraded by Rrp6- or by Dcp2-dependent pathways.[104] As I have previously mentioned, the formation of the Sm-ring and the trimethylguanosine cap both serve as import signals and thus represent an important quality control point that ensures that only properly assembled and modified core snRNPs return to the nucleus.[2] It is worth mentioning that while the Sm-ring is indispensable for the import, the importance of the trimethylguanosine cap varies among individual snRNPs and cell types.[105-107]

After reaching the nucleus, core snRNPs first accumulate in CBs. When snRNP-specific proteins are depleted or the formation of di- or tri-snRNP is blocked, U4, U5 and U6 snRNAs highly accumulate in CBs.[28,29,31,57] This demonstrates the presence of an additional checkpoint that controls the final steps of snRNP maturation, sequesters immature snRNPs and allows only mature particles to enter the splicing reaction. SnRNP sequestration in CBs depends on SART3, which interacts with coilin and thus provides a molecular bridge between snRNPs and coilin.[29] However, the exact molecular mechanism of how SART3 recognizes immature snRNPs is unknown.

Cajal bodies need snRNPs

CBs in cell culture are sensitive to inhibition of transcription, splicing and snRNP biogenesis.[108] First, snRNPs disappear from CBs after transcription and splicing inhibition, followed by CB disassembly shortly after. This shows that constant production and recycling of snRNPs is essential for CB integrity. Recently, our laboratory showed that CBs can be induced in primary fibroblasts that normally lack them, by inhibition of tri-snRNP assembly.[29] In addition, overexpression of coilin does not induce CB formation but overexpression of snRNP components does.[109] Finally, snRNP-specific proteins are potent inducers of CBs when artificially immobilized to chromatin.[110] These results demonstrate that CB formation requires at least 2 components: coilin and snRNPs. Findings that coilin directly interacts with snRNAs *in vivo* and that snRNAs induce coilin aggregation *in vitro* supports this 2-composite model of CB formation.[81,111] In the future, we have to uncover rules that govern and control protein-protein and RNA-protein interaction in the CB microenvironment to reveal the basic principles of how snRNPs drive CB formation.

Final remarks

Many steps in snRNP biogenesis are closely associated with CBs but these microscopically visible CBs are not present in all cell types. This signifies that CBs are not absolutely essential and that snRNPs are able to mature and recycle without them. However, the presence of CBs in embryonic, highly dividing and metabolically active cells shows that
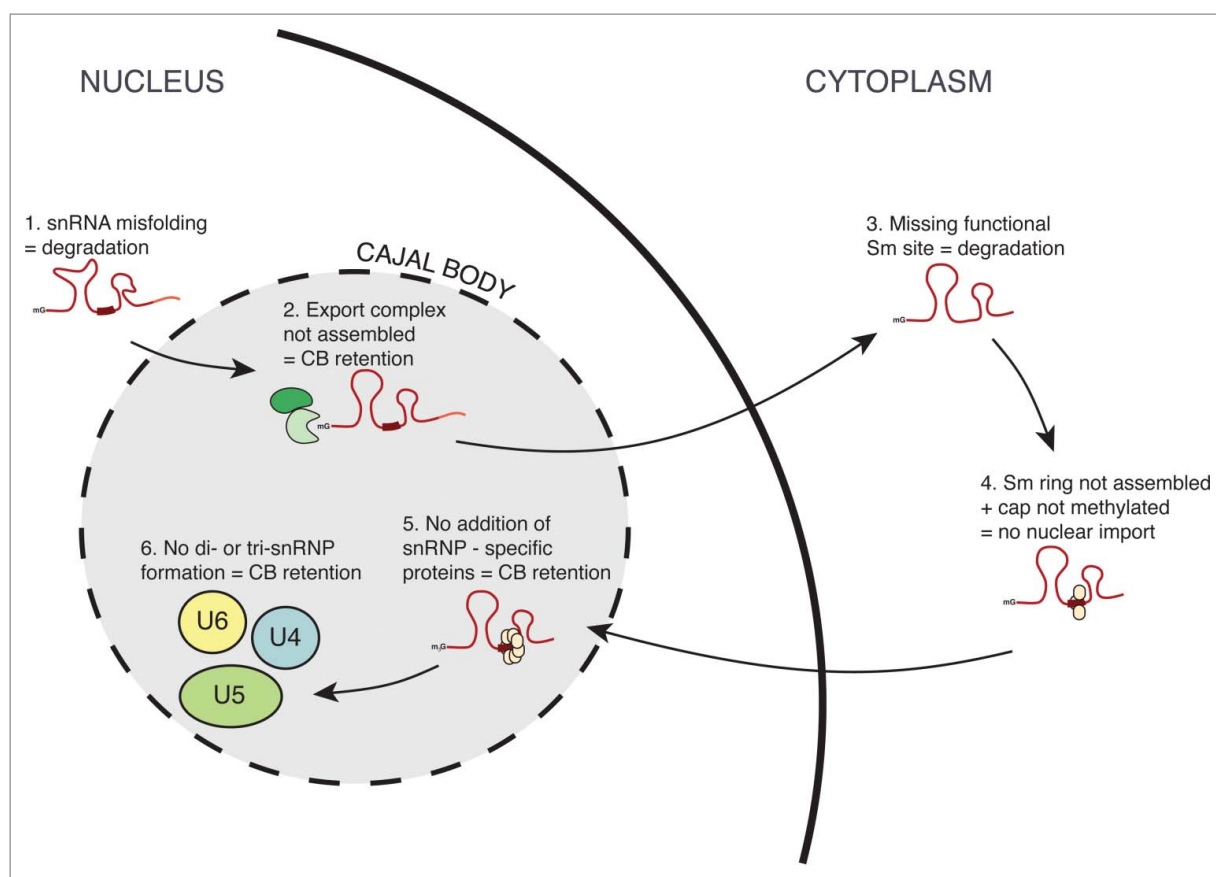
Figure 2. SnRNP biogenesis is closely controlled along the maturation pathway. Misfolded snRNAs are degraded by the exosome/TRAMP complex dependent pathway. Next, formation of the snRNP export complex is monitored and only the properly assembled export complex is transported to the cytoplasm. In the cytoplasm, snRNAs with non-functional Sm-binding site are degraded. Sm-ring assembly and cap trimethylation serve as an additional checkpoint and only properly formed snRNPs are imported back to the nucleus. The core snRNP is targeted to the Cajal body where snRNP-specific proteins are added and di- and tri-snRNPs are formed. If either of these last steps fails, immature snRNPs are retained in the Cajal body.

CBs are important when metabolism is high. Recent evidence that displacement of histone mRNA processing factors from nuclear bodies reduces the efficiency of histone mRNA 3′ end processing shows the importance of nuclear structures and the concentration of factors within them.[112] I conclude that the CB and snRNP are necessary for one another. The concentration of snRNPs in the CB enhances snRNP maturation by providing the appropriate chemical environment as well as the required snRNP biogenesis factors.[31,113,114] In turn, snRNPs promote coilin aggregation and CB formation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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