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Quality control in snRNP biogenesis

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Abstract

snRNPs are key components of the spliceosome. During their life, they are found in the cytoplasm and also in the nucleus, where carry out their function. There are five major snRNPs named according to RNA they contain U1, U2, U4, U5, and U6. Each snRNP consists from RNA, ring of seven Sm or LSm proteins and additional proteins specific for each snRNP. Their biogenesis starts in the nucleus, where they are transcribed. Then they are transported into the cytoplasm. During their cytoplasmic phase, the SMN complex forms the Sm ring around the specific sequence on snRNA and cap is trimethylated. These two modifications are the signals for re-import of snRNA into the nucleus, where they accumulate in the nuclear structures called Cajal bodies (CBs), where the final maturation steps occur.

There are several quality control points during snRNP biogenesis that ensure that only fully assembled particles reach the spliceosome. The first checkpoint is in the nucleus immediately after the transcription, when the export complex is formed. The second checkpoint is in the cytoplasm and proofreads Sm ring assembly. If the Sm ring formation fails, the defective snRNPs are degraded in the cytoplasm by Xrn1 exonuclease. However, it is still unclear, how the cell distinguishes between normal and defective snRNAs. The last checkpoint occurs in CBs. However, signals that target and retain snRNPs in CBs have yet to be described.

In this work, I analyzed the main role of the Sm ring in the quality control of snRNA in the nucleus and the cytoplasm.

First, we identified Sm protein motifs important for targeting of snRNPs into CBs and proposed a model, where Sm proteins play an important role in quality control in CBs.

Second, we explored a role of the component of the SMN complex, Gemin3, in the Sm ring assembly. My data suggest that Gemin3 is involved in unwinding of the secondary structure or snRNA before Sm ring formation.

Finally, we investigated the defective snRNAs which failed to acquire the Sm ring in the cytoplasm. We found that immature snRNAs are localized in P bodies and identified a new role for the LSm1 protein in snRNA degradation.

Introduction

In all cells, the guideline for life is encoded in DNA, where the information is devided into discrete functional units called genes. The main cellular components – proteins, encoded in protein-coding genes, are converted into a protein sequence by transcription and translation. In eukaryotes, these two processes are spatially separated by the nuclear membrane. In the first step, the DNA is transcribed into the pre-mRNA. Before the pre-mRNA is translated, it has to be modified in the nucleus. These modifications are adding a monomethyl cap at the 5´end, removing of non-coding sequences (introns) and joining of coding sequences (exons), polyadenylation at 3´end and sometimes base editing. The removing of introns from pre-mRNA is called splicing. This well-controlled process is catalyzed by the spliceosome, which is a large complex composed from more than 150 proteins but the essential core is formed from 5 small nuclear ribonucleoprotein particles (U1, U2, U4, U5, and U6 snRNPs). These particles are composed of short non-coding, non-polyadenylated RNA, Sm or LSm proteins and proteins, which are specific for each snRNP.

My work is focused mainly on the biogenesis of U1, U2, U4, and U5 snRNPs. They are transcribed in the nucleus by RNA polymerase II and transported into the cytoplasm where Sm proteins are loaded on RNA and form an Sm ring around the specific sequence. After this step, the monomethyl cap is trimethylated, and snRNPs are prepared for transport back to the nucleus, where snRNPs first accumulate in the nuclear structures called Cajal bodies (CBs). However, the precise mechanism of how is the maturation of snRNPs controlled and how are the snRNPs targeted into the CBs is still unknown. Cajal bodies are the place of modification of snRNAs, binding specific proteins and de novo assembly and recycling of U4/U6 di-snRNP a U4/U6·U5 tri-snRNP (Stanek

et al., 2003). When the snRNP is fully maturated is released from the CB into the nucleoplasm, where becomes a part of the spliceosome. Because the splicing is one of the most important processes in the cell and the disturbance of the splicing can lead to disease as a Spinal muscular atrophy or Retinitis pigmentosa (Ruzickova and Stanek, 2016; Pellizzoni et al., 1998), assembly of snRNP has to be under strict control.

The snRNP biogenesis undergoes three major checkpoints. The first checkpoint is in the nucleus after the pre-snRNA transcription. The export complex is assembled on the 5´cap. The export complex is composed of the exportin 1, Cap binding complex and PHAX, which is specific for snRNA (Fornerod et al., 1997; Ohno et al., 2000). If the export complex is not assembled, the snRNA is degraded in the nucleus (Suzuki et al., 2010).

The second checkpoint is in the cytoplasm, where the snRNA is bound by the SMN complex, which is important for Sm ring assembly. If the Sm ring is not formed, snRNA are transported into the P bodies and consequential degraded by the Xrn1 exonuclease (Ishikawa et al., 2014; Shukla and Parker, 2014). P bodies are storage of proteins involved in degradation pathways of mRNA (LSm1, Dcp1, Dcp2, Xrn1, Ago2). However, the mechanism how the defective snRNA are recognized and transported into the P bodies is still unknown. The last study showed that the truncated form of U2 snRNA is uridilated on 3´end by TUT4 and TUT7 enzymes. This modification is specific for RNAs which are convicted of degradation by 3´-5 ´exonuclease DIS3L2 (Ishikawa et al., 2018). This exonuclease is not localized in the P bodies but is spread in the cytoplasm. These experiments show that cell uses more degradation pathways for deprivation of defective snRNAs.

Concerning the importance of snRNP assembly, we decided to look deeper into their biogenesis.

Aims

The primary goal of my project is to gain a deeper insight into the biogenesis of snRNPs, which are critical components of the spliceosomal complex. I focus on three specific aims:

- To decipher the localization signal, which navigates the snRNP into nuclear structures called Cajal body, the place of final snRNP maturation

- To describe the role of the SMN complex component, Gemin3, in the Sm ring formation in the cytoplasm)

- To identify factors responsible for the recognition and degradation of incomplete snRNPs in the cytoplasm.

Material and Methods

In this study, we used microinjection and biochemical methods, such as co-immunoprecipitation (co-IP), western blotting, in vitro transcription and PCR to characterize proteins and snRNA sequences important for targeting into the Cajal bodies. We used siRNA mediated RNA interference for testing the physiological function of proteins of our interest. To analyze the protein-RNA interactions, we utilized RNA isolation and reverse transcription combined with quantitative polymerase chain reaction (RT-qPCR). The secondary structure of all U2 snRNA mutants was analyzed by mathematical modeling. Structure analysis was carried out using the Vienna RNA package (Lorenz et al., 2011).

We complemented these methods with advanced fluorescent microscopy approaches, such as high-content microscopy with automated image analysis and for counting of Cajal bodies, we used the Analysis Scan^R software.

Results

In the first project, we analyzed the sequences and proteins which are important for snRNPs targeting into the nuclear structures called Cajal bodies (CBs). We found out that Sm proteins are essential for this process. We mapped the Cajal body targeting signal into the GR repeats of SmB/B´, SmD1 and SmD3 proteins. We also analyzed the quality control of snRNPs in the CBs and showed that immature snRNPs are accumulated in the CBs. We proposed a model, where Sm proteins play a role in the targeting of snRNPs into CBs and also in their quality control in the CBs.

In the second project, we studied alternative snRNA secondary structure, which was observed during the mathematical modeling of U2 snRNA in my previous project. In this structure, the Sm site is surrounded by an extensive stem, which we named Near Sm site Stem (NSS) and is not observed when the Sm ring is formed. We found out that Gemin3, which is DEAD-box RNA helicase plays important role in the opening this NSS to access the Sm site for Sm ring assembly.

In the third project, we focused on the snRNPs quality control in the cytoplasm. We showed that snRNAs are rapidly accumulated in the cytoplasmic structures called P bodies and degraded afterward when the Sm ring is not assembled properly. We analyzed LSm1 protein, which is a part of 5´-3´ degradation pathway in the cytoplasm. We found out that this protein interacts with snRNAs when the Sm ring is disrupted. When we depleted LSm1 protein and also disrupted the Sm ring, we observed that snRNAs were not accumulated in the P bodies. We proposed a model where the LSm1-7 ring plays a role in the navigating of immature snRNPs into the P bodies and is a part of the quality control of snRNP biogenesis in the cytoplasm.

Discussion

snRNP biogenesis starts in the cell nucleus by snRNA transcription, continues in the cytoplasm, where snRNA acquires the ring of Sm proteins, and then the core snRNP returns to the nucleus, where snRNP maturates and participates in splicing. After reimport to the nucleus snRNPs first appear in CBs where the final steps of their maturation occur (Nesic et al., 2004; Stanek et al., 2003). Despite an important role of CB in snRNP biogenesis, it has not been clear what targets the core snRNPs to CBs. In this first project, we provide several lines of evidence, which Sm and SMN sites on the snRNAs are necessary and sufficient to target snRNAs into CBs.

Previously it has been shown that minimal sequence containing Sm and SMN binding sites is sufficient to bind the SMN complex (Yong et al., 2004; Golembe et al., 2005). It was proposed that this complex is able to facilitate nuclear import of newly assembled core snRNPs and target them via interaction with coilin to CBs (Narayanan et al., 2004). This indicates a role of SMN complex in the Cajal body targeting of core snRNPs. Our experiments showed that the depletion of Sm proteins blocks CB localization of U2 snRNA WT, which contains SMN binding sites. Moreover, the core snRNPs (snRNA with Sm ring) were accumulated in CBs even if the SMN protein was depleted. These data show, that SMN complex is not necessary for targeting of snRNP into the CBs.

In the CBs the core snRNPs have to be captured. Coilin is the main CB protein and is the most prominent candidate, which can interact directly with the core snRNPs. The previous studies showed the direct interaction between coilin and Sm proteins via its Sm-fold (Toyota et al., 2010; Xu et al., 2005). However, the interaction is enhanced and stabilized by the C-terminal tails of Sm proteins (Xu et al., 2005). The C-terminus of coilin contains a Tudor domain

(Shanbhag et al., 2010), which in other proteins interacts with methylated arginines (Pek et al., 2012). We have shown that deletion of GR repeats reduces Sm protein localization to CBs. Thus, we can speculate that the coilin Tudor domain binds dimethylated arginines of GR repeats found in the C-termini of SmB/B´, SmD1 and SmD3. However, it was shown before, that the isolated coilin Tudor domain did not exhibit any dimethylated arginine binding activity in vitro (Shanbhag et al., 2010) leaving the molecular mechanism of coilin-snRNP interaction resolved. The iCLIP data showed direct binding of coilin to snRNAs. This interaction likely provides an additional signal for CB localization of snRNAs (Machyna et al. 2014).

The Cajal bodies are a place of the final maturation of the snRNPs (Tanackovic and Kramer, 2005; Stanek et al., 2003). Novotný and colleagues have previously shown that the inhibition of the final steps in the U4, U5 and U6 snRNP assembly pathway leads to sequestration of immature snRNPs in the CBs (Novotny et al., 2015). Here, we observed the same phenotype in the case of microinjection of U2ΔSLI snRNA, which does not interact with the SF3a complex. In contrast, when we deleted the Sm site in the U2ΔSLI mutant, this defective snRNA did not accumulate in CBs. Based on our results that the Sm ring serves as an essential CB targeting signal, we propose a model that the exposed Sm ring serves as a CB retention signal. We hypothesize that interactions of CB proteins with the unprotected Sm ring represent the molecular basis of the cellular mechanism controlling final steps of snRNP assembly.

Previous studies showed that SMN complex plays an essential role in the snRNP biogenesis, especially in the Sm ring assembly but the molecular function of individual components is unclear (Pellizzoni et al., 1998; Massenet et al., 2002). Our modeling of U2 snRNA secondary structure using RNAfold program

predicts an extensive base-pairing of sequences around the Sm site, which we called Near Sm site Stem (NSS). This secondary structure is opened when the Sm ring is assembled. Previous experiments showed that the SMN complex is essential for this process (Paushkin et al., 2002). Our data show that depletion of the Gemin3 decreases snRNA accumulation in the CBs. However, the role of Gemin3 in the Sm ring assembly is still unknown. The Gemin3 was annotated as a DEAD-box RNA helicase. The main function of the RNA helicases is to unfold the secondary structures of RNAs using the energy from ATP. We prepared the mutant U2 stableNSS, where the NSS was more stable in comparison with WT and this mutant was not efficiently transported to the nucleus, which indicates that the structure around the Sm site plays a role in Sm ring assembly. Contrary, mutant U2noNSS, where the NSS was opened, was transported into the CBs when the Gemin3 was depleted. This finding strongly suggests that Gemin3 is important for unwinding the NSS for the accessibility of the Sm site for Sm ring formation.

My previous data showed an important role of Sm ring in the targeting of snRNPs into the CBs. When the Sm ring formation is disrupted snRNAs are accumulated in the cytoplasm. The previous study showed that truncated form of U1 snRNA is accumulated in the cytoplasmic foci called P bodies and are degraded by the Xrn1 exonuclease (Ishikawa et al., 2014; Shukla and Parker, 2014). We observed the same phenotype for all endogenous snRNA (U1, U2, U4, and U5) when we disrupted Sm ring assembly. However, the recognition of immature snRNPs and their targeting into the P bodies is still unknown. P bodies are storage of many factors involved in RNA degradation such as exonuclease Xrn1 or decapping enzymes Dcp1 and Dcp2. We tried to find the protein which is responsible for navigating of defective snRNAs into the P bodies. The Lsm 1-7

ring is responsible for stabilizing of decapping enzymes on mRNA intended for degradation. We provide several lines of evidence that LSm1 play a role in the localization of snRNAs without Sm ring into the P bodies. First, we showed that LSm1 protein binds the snRNAs after the depletion of Sm protein. Furthermore, the reduction of LSm1 prevents the localization of defective snRNAs into the P bodies. Our data suggest that LSm1-7 ring play a role in snRNA degradation pathway. However, the binding mechanism of the LSm1-7 ring on snRNA is unknown. The binding site for the LSm1-7 ring is composed of 8 uridines (Zhou et al., 2014). A recent study has shown that the truncated form of U2 snRNA (U2-tfs) are uridylated on 3´end by TUT4 and TUT7 (Ishikawa et al., 2018), which can create LSm binding site. Taken together our data suggest a new role for the LSm1-7 ring in snRNA degradation pathway. However, the precise mechanism remains unclear.

Conclusion

In this work, I focused on the snRNP biogenesis. snRNPs are key components of the spliceosome, which catalyzes the splicing of pre-mRNA. My project is separated into the three chapters undertake snRNP assembly and quality control of their maturation in the nucleus and the cytoplasm.

In the first project, I studied the part of snRNP biogenesis, where the snRNPs are targeted into the nuclear structures called Cajal bodies, where the final maturation steps occur. We found out that Sm proteins navigate snRNPs into these structures and mapped this Cajal body targeting signal to GR repeats of SmB/B', SmD1 and SmD3. Our experiments also showed that incomplete snRNPs are more accumulated in the CBs comparing with the WT snRNAs. Based on my experiments we established a model, where Sm proteins are necessary for targeting of snRNP into CBs and also play a role in their quality control in the CBs.

In the second project, I studied alternative snRNA secondary structure, which was observed during the mathematical modeling of U2 snRNA in my previous project. In this structure, the Sm site is surrounded by an extensive stem, which we named Near Sm site Stem (NSS) and is not observed when the Sm ring is formed. It is known that SMN complex plays the main role in Sm ring assembly. We depleted the component of the SMN complex, Gemin3, which is DEAD-box RNA helicase and observed less accumulation of snRNAs in CBs. We propose a model, where the Gemin3 can play a role in unwinding the NSS and opens this structure for Sm ring assembly.

In the third project, I focused on the quality control of snRNA biogenesis in the cytoplasm. I showed that disruption of Sm ring assembly leads to accumulation of snRNAs in the cytoplasmic structures called P bodies and their

consequential degradation by Xrn1. In this degradation pathway, many proteins are involved. I focused on LSm1-7 ring which plays a role in stabilizing of decapping enzymes Dcp1 and Dcp2 and identified a new role of Lsm1 protein in the navigating of defective snRNAs into the P bodies, where are decapped and degraded by Xrn1.

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Curriculum vitae

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Bachelor thesis: Factors important for Cajal body formation
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Poster: Sm - ring dependent targeting of U snRNA into Cajal bodies
2017: RNA 2017, 22nd Annual meeting of RNA society, Prague
Poster: Sm - ring dependent targeting of U snRNA into Cajal bodies
2017: International Congress of Cell Biology (ICCB 2016)
Poster: Sm - ring dependent targeting of U snRNA into Cajal bodies
Awarded: The best poster
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Poster: The Sm-core mediates the retention of partially-assembled spliceosomal snRNPs in Cajal bodies until their full maturation

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