HOKKAIDO UNIVERSITY

Title	Balancing RNA processing and innate immune response: Possible roles for SMN condensates in snRNP biogenesis.
Author(s)	Maita, Hiroshi; Nakagawa, Shinichi
Citation	Biochimica et biophysica acta. General subjects, 1869(3), 130764 https://doi.org/10.1016/j.bbagen.2025.130764
Issue Date	2025-01-16
Doc URL	https://hdl.handle.net/2115/97370
Rights	© 2025. This manuscript version is made available under the CC-BY-NC-ND 4.0 license https://creativecommons.org/licenses/by-nc-nd/4.0/
Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	revised_manuscript_maita.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Balancing RNA Processing and Innate Immune Response: Possible Roles for SMN Condensates in snRNP Biogenesis

Hiroshi Maita[1,2*] and Shinichi Nakagawa[1,2]

[1] Graduate School of Life Science,

[2] Faculty of Pharmaceutical Sciences,

Hokkaido University, Sapporo, Japan 060-0812

[*]Corresponding author: Hiroshi Maita

Kita12 Nishi6, Kita-ku, Sapporo, Hokkaido, Japan, 060-0812
Phone: 011-706-3921
E-mail: maimai@pharm.hokudai.ac.jp

Abstract

Biomolecular condensates like U-bodies are specialized cellular structures formed through multivalent interactions among intrinsically disordered regions. U-bodies sequester small nuclear ribonucleoprotein complexes (snRNPs) in the cytoplasm, and their formation in mammalian cells depends on stress conditions. Because of their location adjacent to P-bodies, U-bodies have been considered potential sites for snRNP storage or turnover. SMN, a chaperone for snRNP biogenesis, forms condensates through its Tudor domain. In fly models, defects in SMN trigger innate immune responses similar to those observed with excess cytoplasmic snRNA during viral infection in mammalian cells. Additionally, spinal muscular atrophy (SMA), caused by SMN deficiency, is associated with inflammation. Therefore, SMN may help prevent innate immune aberrant activation due to defective snRNP biogenesis by forming U-bodies to sequester these molecules. Further studies on U-body functions may provide therapeutic insights for diseases related to RNA metabolism.

Keywords: U-body, intrinsically disordered region, SMN, Tudor domain, symmetrical arginine dimethylation, Cajal body, Coilin

1. Introduction

1.1 Physiological Roles of Biomolecular Condensates

Biomolecular condensates are cellular characteristic structures that reflect the distinctive behavior of proteins and RNA. Intrinsically disordered regions (IDR), which are representative of "non-domain" regions in protein sequences, often contribute to the formation of such condensates with RNA [1–5]. These IDRs enable weak, multivalent interactions that drive phase separation, concentrating biomolecules into specialized compartments. This compartmentalization enhances reaction efficiency and stabilizes stored molecules by protecting them from degradation. Moreover, it increases the fidelity of reactions by isolating molecules in specific compartments to prevent aberrant crosstalk between simultaneously activated pathways. However, the exact cellular processes that require such compartmentalization for fidelity are not fully understood. This review focuses on the role of U-body [6], a cytoplasmic condensate involved in the biogenesis of small nuclear ribonucleoprotein complex (snRNP) (Fig. 1). We propose that U-bodies may maintain the fidelity of the innate immune response by sequestering small nuclear RNA (snRNA) with the help of SMN to prevent accidental activation of the cytosolic RNA sensors. To support this hypothesis, we first provide an overview of U-bodies and snRNP biogenesis pathway, followed by a detailed explanation of the quality control mechanism within this pathway. In the subsequent section, we discuss the molecular function and behavior of SMN and present a model of its function. Based on this hypothesis, we further explore the physiological role of the U-body in light of recent publications. Finally, we examine this hypothetical role of the U-body and SMN in the context of findings in neuromuscular disease.

1.2 U-bodies, Mysterious Condensates in the Cytoplasm

U-bodies are cytoplasmic foci that contain U snRNA and other components required for snRNP biogenesis. However, U-body formation is limited to specific conditions. The first report of U-body formation came from observations in Drosophila oocyte [6]. Although this study aimed to investigate the localization of U7 snRNP, a component of the nuclear histone locus body (HLB), it unexpectedly found that U7 snRNP localized in the cytoplasm of giant polyploid nurse cells. This discovery revealed that U snRNPs, typically found in the nucleus, were enriched in cytoplasmic foci, later referred to as U-bodies. Further analysis showed that these U-bodies are formed in various cell types, including brain, gut, and testis. Moreover, U-bodies accumulated other U snRNPs and were consistently adjacent to P-bodies, another type of cytoplasmic granules that are constitutively formed for mRNA decapping and degradation [1,5], although not all P-bodies are located near U-bodies. Notably, U6 snRNA, which is usually restricted to the nucleus, was also observed in U-bodies.

The reason why different cell types form U-bodies remains unclear. In mammalian cells, stress conditions such as amino acid starvation and bacterial infection, both of which inhibit translation initiation, trigger the formation of U-bodies [7]. U-bodies in fly nurse cells have also been reported to respond to nutrient stress [8]. However, the detailed mechanism by which these stress conditions impair translation initiation and lead to U-body formation remains unclear. Moreover, these observations raise the question of why such a response is necessary.

1.3 Overview of snRNP Biogenesis

Eukaryotic cells require intron splicing to express most genes. The spliceosome, assembled on an intron from its subunits snRNPs, catalyzes the splicing reaction [9–11]. Five distinct snRNPs are required to assemble a major spliceosome, each containing different uridine-rich snRNAs (U snRNA), U1, U2, U4, U5, and U6, along with specific binding proteins. These U snRNAs are essential components of the spliceosome, serving as scaffolds and a catalytic center for the transesterification steps of the splicing reaction [9–11]. The spliceosome assembles on each intron to conduct splicing, and because human genes contain an average of seven to eight introns each

[12], cells must produce a large number of snRNPs. Thus, maintaining the snRNP assembly pathway is crucial for normal gene expression. To produce snRNPs, snRNAs follow a complex pathway that includes an unexpected cytoplasmic stage (Fig. 2) [13–15], despite the fact that their transcription and function occur in the nucleus. Newly transcribed snRNAs (except U6, which is transcribed by RNA polymerase III) are exported to the cytoplasm, where they undergo modifications, such as acquiring a ring-shaped Sm proteins complex composed of seven Sm proteins (B/B', D1, D2, D3, E, F, and G) on the Sm-binding sequence (Sm-site) and hypermethylation of the 5' cap structure. The Gemin complex, which consists of Survival Motor Neuron (SMN), Gemin2-8, and UNRIP/STRAP[13], serves as a chaperone to assemble the heptameric Sm protein complex on snRNA. Partially assembled sub-complexes of Sm proteins are formed with the assistance of the 20S methylosome containing pICln. Hypermethylation of the 5' cap is mediated by TGS1, which also occurs in the cytoplasm [14]. Acquiring both the Sm-ring and a tri-methyl cap (TMG cap) is thought to serve as a signal for snRNA nuclear import [14], although the role of TMG cap in nuclear import varies across species and is not conserved in yeast [16,17]. Once inside the nucleus, snRNPs accumulate in Cajal bodies (CB), where further modifications occur on snRNA guided by small CB-specific RNAs (scaRNAs) [18–20]. These modifications are crucial for the correct splice site selection and the efficient assembly and activation of the spliceosome [19,20]. Additionally, the 3' end of snRNA is processed by TOE1, 3'-exoribonuclease that is activated by Sm complex and the tri-methylated 5' cap of snRNA [21]. Fully modified snRNPs then undergo stepwise assembly to form a mature snRNP complex that is ready for spliceosome assembly. Therefore, the Cajal body is considered the final maturation site for snRNP before supplying fully mature U1, U2, and U4/U6.U5 tri-snRNPs for splicing. The snRNP biogenesis pathway is conserved from yeast to humans, and yeast strains deficient in shuttling snRNA between the nucleus and cytoplasm exhibit splicing defects due to defective spliceosomes that incorporate immature snRNA. This suggests that the cytoplasmic stage of snRNP biogenesis is essential to maintaining spliceosome integrity [17].

2. The Cytoplasmic Stage of snRNP Biogenesis and Quality Control

2.1 Nuclear Export and Capture of snRNA by the Gemin Complex

To achieve the nuclear export of nascent snRNA in the early stage of snRNP biogenesis, the CRM1-dependent transport system operates with an export complex composed of the cap-binding complex (CBC) and PHAX, formed on the monomethylated 5' cap [14]. CBC directly binds to the cap structure, while PHAX acts as an adaptor that links CBC and CRM1 in a phosphorylation-dependent manner [14,22]. The export complex is restricted to short RNAs with a 5'cap, such as snRNA, because the hnRNP C tetramer blocks PHAX loading by binding to CBC when the RNA length exceeds 300 nucleotides [23]. Once the complex reaches the cytoplasm, a cytoplasmic phosphatase dephosphorylates PHAX, triggering the disassembly of the export complex (Fig. 3, left) [24]. After the disassembly of the export complex, released snRNA is captured by the Gemin complex. Biochemical and structural analysis have shown that the WD40 domains in the N-terminal region of Gemin5, the largest subunit of the Gemin complex, capture snRNA through direct binding to both the 5' cap and Sm-site sequence [25]. Therefore, snRNA's entry into the cytoplasm is strictly regulated by leveraging key features such as length, 5' cap, and Sm-site. Interestingly, Gemin5 has been identified as part of a complex with NCBP1, which forms CBC with NCBP2, suggesting that Gemin5 may capture exported snRNA before the export complex disassembly through interaction with NCBP1 [26]. Affinity-purified Gemin5 from the lighter cytoplasmic fraction of glycerol gradient sedimentation revealed its association with PHAX, CBC, Gemin3, and Gemin4 but not with other Gemin complex components, including SMN [27]. This complex is co-purified with all tested snRNA, indicating that the Gemin 3/4/5 complex immediately surveys CBC-labeled RNA upon its arrival in the cytoplasm to capture snRNA.

2.2 Formation of the Sm-Ring Complex

Before snRNA acquires the Sm-ring complex, this ring is partially assembled with the help of pICln and the methylosome (Fig. 3, right), which contains PRMT5 and MEP50 [28]. pICln binds nascent SmD1, SmD2, and SmB/B' polypeptides adjacent to the ribosome [29] and brings these proteins to the methylosome, where pICln forms an incomplete ring-shaped complex with Sm proteins by fitting itself into the ring based on its protein fold, which is similar to Sm proteins [30,31]. PRMT5, an arginine methyl transferase, in the methylosome symmetrically dimethylates Sm proteins at arginine residues in the RG motif (composed of arginine and glycine repeats) in the extended C-terminal regions of these Sm protein subtypes. The Gemin complex containing SMN interacts with the incomplete pICln-Sm D1/D2/D3 complex and another complex of pICln and SmB to assemble the final ring-shaped complex with SmE/F/G. SMN binds the symmetrically dimethylated arginine (sDMA) of Sm proteins through its Tudor domain, suggesting that arginine dimethylation introduced at the methylosome may accelerate the transfer of the pICln-Sm complex to the Gemin complex. In this intermediate complex between Gemin and Sm proteins, Gemin2 replaces pICln in the ring and blocks spontaneous RNA binding by covering the center region of the incomplete Sm-ring using its N-terminal domain [32]. The center of the Sm-ring complex is the site that directly binds nucleotides in the conserved Sm-site sequence. Although each Sm protein specifically recognizes one or two nucleotides within the Sm site, the sequence specificity of the Sm-ring formation is not particularly stringent, potentially leading to the spontaneous deposition of the ring on non-target RNA. Because Sm-ring deposition could stabilize RNA [33], the N-terminal domain of Gemin2 plays a crucial role in preventing undesired RNAs from accidentally acquiring the Sm-ring. Therefore, similar to snRNA, Sm proteins are also carefully handled from their production until the completion of their assembly on snRNA.

2.3 Quality Control of snRNA in the Cytoplasm

Given Gemin5's role in distinguishing snRNA from other RNA species through its binding to the 5' cap and Sm site, a shortage of either snRNA or Sm protein could stall the Gemin complex. Additionally, defective molecules, such as truncated snRNA or misfolded Sm proteins, may affect the complex processing pathway of snRNP assembly. Therefore, in addition to distinguishing the genuine substrates mentioned above, cells must also possess mechanisms to discard or delay pathways for aberrant substrates.

Indeed, such pathways have been suggested. The Gemin complex captures U1 snRNA that lacks the 3' end sequence, including the Sm-site, likely due to erroneous 3' end processing. This truncated U1 snRNA accumulates in P-bodies, exhibits a shorter half-life, and reduced expression of SmB protein leads to the accumulation of normal U1 snRNA in P-bodies [27]. Notably, the same study showed that the first transcribed nucleotide of truncated U1 snRNA was methylated, similarly to the Cap2 form of mRNA [34], which may serve as a marker to degrade the labeled snRNA retained in the cytoplasm longer than normal snRNA. Degradation pathways for these RNAs have been identified by analyzing snRNA defective in Sm-ring assembly. These snRNAs become substrates for decapping and degradation by exonucleases DIS3L2 and Xrn1, which degrade RNA in both 5'-to-3' and 3'-to-5' directions, respectively [35,36]. Similarly, variant snRNAs with divergent 3' end sequences that are defective in the 3' end processing by TOE1 also become targets for the nuclear exosome [37]. Inhibition of Sm-ring deposition through reduced SMN expression causes the accumulation of degradation intermediates as cytoplasmic foci that overlap with P-bodies [38,39]. These findings suggest that defects in Sm complex loading trigger snRNA accumulation in P-bodies for degradation, with the Gemin complex acting as a surveillance system to ensure snRNA integrity.

2.4 Strict Regulation of the Supply System of Sm Proteins

Additionally, cells strictly regulate Sm protein levels. A reduction in SMN levels causes

downregulation of Sm protein mRNA through exosome-mediated degradation, following the tailback of Sm proteins on pICln, though it is still unclear how the exosome specifically recognizes this mRNA [38]. This regulation may reflect a mechanism to avoid Sm protein aggregation, as reducing pICln levels causes Sm proteins to aggregate, which are subsequently degraded via autophagy [38]. In addition, overexpression of pICln and Gemin2, which causes the cytoplasmic retention of Sm proteins, results in toxicity in flies, further supporting the importance of the stoichiometry between Sm proteins and their chaperon proteins [40,41]. Interestingly, autophagy-degraded Sm proteins are limited to SmB, D1, D2, and D3, which pICln directly interacts with at the ribosome to form the initial methylosome complex [29,31]. ULK1, a kinase that initiates autophagy, phosphorylates pICln, affecting the structure of the 6S complex containing pICln and Sm proteins. This phosphorylation enhances the link between the partially formed Sm complex and the Gemin complex [42]. Thus, ULK1 could be a key factor in detecting the status of the Sm protein complex. If Sm protein levels exceed pICln levels, ULK1 may be displaced from pICln by competition, initiating autophagy near pICln to eliminate Sm protein aggregates. This suggests that cytoplasmic Sm protein levels are strictly regulated from ribosome to snRNA loading, preventing the spontaneous stabilization of non-target RNAs, such as viral RNA [43]. In summary, cells prepared pathways to discard excess or defective snRNA and Sm proteins, which raises the question: why does the cell have such a complex pathway for snRNA? This may be explained by considering the origin of snRNA and the innate immune system.

3. The Evolutionary Origin of snRNAs and the Innate Immune System

3.1 Innate Immunity and Cellular Mechanism to Prevent Its Aberrant Activation

The innate immune system has evolved to recognize pathogens, specifically foreign RNA, through pathogen-specific molecules. In the cytoplasm, double-stranded RNA (dsRNA) is identified as a marker of viral infection because cellular mRNA tightly suppresses dsRNA [44]. When dsRNA accumulates in cells, it activates PKR, halting translation initiation by phosphorylating eIF2α. This response rapidly releases mRNA from polysomes, leading to the formation of stress granules (SGs) that transiently store mRNA under stress conditions. SGs also play an active role in innate immune signaling [45]. Viral RNAs that activate PKR also stimulate the cytoplasmic RNA sensors MDA5 and RIG-I, which trigger a pro-inflammatory response. The accumulation of activated RIG-I in SGs suggests that SGs act as signaling hubs for this immune response. Interestingly, reduced ADAR1 expression, which binds to and dissolves dsRNA, results in spontaneous SG formation via PKR, emphasizing that cells must avoid excessive dsRNA and prevent aberrant activation of the innate immune system [45]. Considering their tendency to form complex secondary structures and evolutionary background, snRNA is an intriguing ligand for cellular RNA sensors in the innate immune system.

3.2 Group II Introns, the mobile Elements as an Origin of snRNA

The evolutionary origin of snRNA is considered to be linked to group II introns [46,47]. A comparison of the secondary structures of catalytically important regions shows similarities with the corresponding parts of group II introns. The spliceosome is a ribozyme that catalyzes reactions using an RNA-based catalytic core. Biochemical reconstitution assays using only synthetic RNA components demonstrated that the transesterification reaction could occur without protein components, further supporting this hypothesis [48]. Additionally, reconstitution of the spliceosome using U6 snRNP containing sulfur substitutions revealed that snRNA holds catalytically essential divalent metal ions in the same positions as group II introns [49,50]. Finally, recent cryoEM structural analyses of the spliceosome have revealed that the splicing reaction occurs in a catalytic center formed by snRNA, consistent with that the spliceosome functions as a ribozyme [11,51]. The structural and mechanistic similarities between snRNAs and group II introns support the idea that snRNAs evolved from group II introns. Group II introns are selfish

genetic elements that may have originated from mitochondrial symbiosis, with their transposition potentially causing harmful effects on the host genome. The presence of multiple copies of group II introns in the host genome may have caused cells to become dependent on their splicing machinery. This evolutionary pressure may have led to cells capturing the catalytic activity of group II introns without further transposition, resulting in ancient cells evolving to maintain group II introns into divided short RNAs. This may have given rise to the current snRNAs, which are catalytically inactive but become active when combined under cellular regulation. However, the free short snRNAs could interfere with normal cellular processes, but more critically, they could trigger the innate immune response. Therefore, a specialized pathway for snRNP biogenesis may have evolved to prevent the accidental accumulation of immature snRNAs.

3.2 **The Potential of snRNA to Trigger the Innate Immune System**

Recent studies have demonstrated that cytoplasmic accumulation of snRNA has the potential to activate the innate immune system. One report showed that ionizing radiation, used in cancer therapy, induces interferon (IFN) signaling, leading to growth arrest and cell death. This IFN signaling is triggered by the cytoplasmic accumulation of snRNA, which forms a complex with RIG-I, leading to activation of IFN signaling [52]. Another study revealed that cells infected with influenza or respiratory syncytial virus exhibit elevated expression of U1 snRNA, particularly a subtype of U1 snRNA transcribed from the pseudo-U1 gene RNVU1-18. The upregulation of RNVU1-18 is required for host defense, as it induces IFN signaling through snRNA binding to TRIM25, an E3 ubiquitin ligase that forms a complex with RIG-I, activating downstream signaling by ubiquitinating RIG-I [53]. Thus, U1 snRNA may function as a ligand for the RIG-I pathway, contributing to the innate immune response during viral infection. Both studies also demonstrated that the synthetic fragments containing the stem-loop regions of U1 snRNA are sufficient to activate RIG-I, suggesting that snRNA's unique secondary structure makes it a suitable substrate for cytoplasmic RNA sensors. Additionally, transfected exogenous snRNA synthesized *in vitro* can induce an innate immune response through the PKR pathway in the absence of RNA modifications [54]. These findings further highlight the necessity of a specialized pathway to process snRNA and prevent it from accidentally triggering the innate immune system.

4. The Molecular Functions and Behavior of SMN

4.1 SMN, the Master Regulator of snRNP Biogenesis Forms Multiple Condensates

To understand the role of U-body from the perspective of the innate immune system, it is helpful to consider the molecular function of SMN, as this protein provides the molecular basis for condensate formation. The SMN (survival motor neuron) protein, the gene implicated in spinal muscular atrophy (SMA), has been extensively studied to elucidate its disease mechanism. SMN is a key factor in snRNP biogenesis, functioning as a chaperone for snRNP assembly in the cytoplasmic pathway and escorting snRNPs to the nuclear Cajal body. As a result, SMN needs to shuttle between the nucleus and cytoplasm to maintain the chaperone cycle, and a unique feature of this shuttling is its ability to form condensate in both the nucleus and cytoplasm. In the nucleus, SMN interacts with Coilin, the major structural component of Cajal bodies, to form these nuclear condensates. SMN also forms Gems (Gemini of Cajal bodies) in the nucleus of mammalian cells, which is often associated with Cajal bodies but can exist independently. However, Gems do not contain Coilin and most of snRNPs [55], unlike Cajal bodies. Overexpression of Gemin3 induces the formation of this type of SMN foci, which contain only Gemin complex proteins, even in the cytoplasm of flies [56]. In stark contrast, U bodies are cytoplasmic condensates that form under specific conditions or in certain cell types and contain snRNPs (Fig. 1). While both types of condensates share some similarities, their formation mechanisms and physiological significance remain unclear. While the Coilin gene and Cajal body formation are not essential for spliceosome assembly, the mechanisms of Cajal body assembly attracted interest, likely because these subnuclear structures are constitutively formed in well-studied cell lines.

In contrast, since U-body formation occurs only under specific conditions, the molecular basis of the U-body formation is not fully understood. However, some studies suggest that the theoretical basis of the U-body formation is similar to that of Cajal body formation in terms of the driving force of phase separation. In early studies that identified U-bodies in Drosophila oocytes, the authors investigated whether sDMA modification of Sm proteins is required for U-body formation. In Drosophila, the dart5 gene, a homolog of PRMT5, was found to reduce sDMA modification in Sm proteins [57]. A dart5 mutant fly was unable to form U-bodies [6], suggesting that sDMA is required for U-body formation. Additionally, SMN mutants with C-terminal domain mutations also lacked U-body formation [58]. Given that dart5 and SMN mutants exhibit synthetic lethality [57], their common deficiency in U-body formation suggests that SMN-sDMA interactions play a role in both U-body formation and snRNP biogenesis. All fly homologs of the Gemin complex also accumulate in U-bodies, further supporting the idea that SMN and the Gemin complex are key determinants in U-body formation [59]. The reason why nurse cells and oocytes form U-bodies remains unclear, though higher SMN expression levels may cause condensate formation. An early study found that overexpression of an SMN mutant lacking the N-terminal 27 amino acids caused the accumulation of snRNA and Sm proteins in cytoplasmic foci, suggesting that transient condensation may serve to sequester delayed snRNP maturation intermediates [60], although it is unknown if the foci are adjacent to P-bodies as seen for U-bodies. Similar cytoplasmic SMN foci are also observed in the wild-type protein when SMN expression levels are excessively high [61], indicating that SMN may have an intrinsic ability to form large condensates once it reaches a threshold concentration. This property might also explain the formation of cytoplasmic foci composed of defective snRNPs or truncated snRNAs. These properties of SMN are further explored below in light of its molecular functions and domain structure.

4.2 The YG-Box as an Oligomerization Domain and Its Regulation

Despite its importance, the overall structure of SMN has not yet been fully solved (Fig. 4A) [62]. Due to its aggregation-prone nature, which aligns with its tendency to form condensate in cells, crystallization of the full-length SMN protein may be challenging. The only well-characterized domain in SMN is the Tudor domain; other protein regions are predicted to be disordered. Structural variability in disordered regions may cause another problem in the structural analysis, although two helices are predicted in the N-terminal region and the YG-box predicted by AlphFold (AF-Q16637-F1) [63]. These predicted helices may reflect the conditional folding, possibly based on a protein binding or a post-translational modification [64,65]. These unfolded, disordered regions are divided based on their amino acid composition and protein-protein interaction properties. These regions include the Gemin2-binding domain and the YG-box, which mediates oligomerization. Oligomerization within the YG-box is a conserved function. Detailed analysis using human and fission yeast SMN proteins revealed that SMN oligomerization occurs via a “ dimers of dimers” model, resulting in oligomers ranging from tetramers to octamers, facilitated by the glycine zipper in the YG-box [66,67]. Further studies showed that the tetramer formed by the SMN and Gemin2 complex has two binding surfaces, enabling self-interaction and higher-order organization of SMN [68]. The N-terminal portion of SMN likely modulates its solubility, limiting multimerization at physiological concentrations of the SMN and Gemin2 complex, which typically ranges in the micromolar range [66,68]. In addition to its interaction with Gemin2, RNA can bind to the N-terminal exon 2b region of SMN, and this RNA binding was demonstrated using different sequences, suggesting that this interaction is not limited to specific sequence [69,70]. The exon 2b region of SMN may also mediate self-interaction with the exon 4 region [71]. Therefore, these RNA binding and self-interaction may regulate YG-box-dependent oligomerization, which suggests that the N-terminal domain likely switches between two conformations: one suited for solubilized dimers and another for condensed multimers. A

mutant fly carrying a mutation that disrupts multimerization exhibited severe locomotor defects and reduced lifespan, indicating the physiological importance of SMN oligomerization [68]. Additionally, many SMA-associated mutations are found within the oligomerization domain [72]. However, when and where SMN forms multimer in the cell remains unclear.

4.3 Tudor Domain, a Key Region for Phase-Separated Condensate Formation

Aside from YG-box-mediated multimerization, the role of the Tudor domain in phase-separated condensate formation was explored using engineered SMN protein [73]. In their study, different regions of SMN—N-terminal, central, and C-terminal—were fused to Cry2, a light-activated dimerization domain, to test their ability to form phase-separated droplets upon light exposure. Interestingly, only the central region of SMN, which includes the Tudor domain, formed light-induced phase-separated droplets. The ability to form droplets was abolished when mutations that disrupted sDMA binding were introduced into the Tudor domain, suggesting that Tudor-sDMA interaction drives phase separation. Other Tudor domains from different proteins also formed droplets, though their dependency on sDMA or asymmetrical DMA (aDMA) differed across Tudor domains, highlighting Tudor-sDMA interactions as a key mechanism in condensate formation. Importantly, inhibiting PRMT5 with a chemical compound disrupted the association between the Cajal body and Gems. Since Coilin is another sDMA-modified protein associated with SMN, this finding suggests that Tudor-sDMA interactions among SMN, Sm protein, and Coilin are necessary to maintain the spatial proximity of these components within the Cajal body. In the absence of these linking interactions, the separation of Gem from the Cajal body may indicate that Gem is assembled based on a different mechanism independent of Tudor-sDMA interactions.

4.4 Coordination of YG-box and Tudor Domain

This also raises another question: how does SMN dissociate from the Cajal body under normal conditions when sDMA is sufficiently present? Coilin and SMN should theoretically remain bound through Tudor-sDMA interactions. However, Courchaine et al. made a critical observation: Coilin and SMN occupy distinct regions within the Cajal body, as shown by super-resolution microscopy (SIM) [73]. In addition, in our own observation using SIM, we found that the relative positioning of SMN and Coilin correlates with the size of the Cajal body. We also observed that harmine, a beta-carboline alkaloid, induces the transient translocation of Coilin to the peri-nucleolar compartment, which is induced by nucleolar stress while having little effect on the localization of SMN within Gems [61]. Since harmine's effects are reversible, we could track Cajal body reformation after removing harmine. During this recovery period, smaller Cajal bodies appeared as mixed SMN-Coilin foci, while larger Cajal bodies that emerged after longer recovery times showed distinct yet connected structures—Cajal bodies labeled with Coilin and Gems with SMN. This suggests that the gradual accumulation of SMN in Cajal bodies eventually leads to Gem formation. Overexpression of an SMN Y272C mutant, which disrupts YG-box function, impaired normal separation processes, resulting in irregular-shaped nuclear structures containing both SMN and Coilin. Taken together, we proposed that YG-box-dependent multimerization plays a role in assembling Gems [61].

4.5 A Model for Switching SMN Function

Since fission yeast SMN lacks the Tudor domain, the Tudor-sDMA pathway involved in forming phase-separated condensates may be an evolutionary addition to SMN, suggesting that its essential molecular function as a chaperone in snRNP assembly relies on its oligomerization ability of the YG-box. This ability is combined with its capacity to bind the Gemin complex, Sm proteins, and snRNA [74,75]. Consistent with this hypothesis, sDMA modification of Sm proteins has been shown to be dispensable for snRNP assembly in flies [57]. Therefore, SMN's fundamental role as an assembly chaperone is to enhance encounters between Sm proteins and

snRNA by concentrating them in multimerization-driven condensates (Fig. 4B). Since SMN's oligomerization is likely modulated by its N-terminal domain, prolonged binding of Gemin2 and assembled snRNPs may lead to the release of the snRNP-SMN complex from the multimer. Based on this, we hypothesize that Tudor-sDMA interactions may weaken SMN's multimerization properties (Fig. 4B). SMN likely alternates between two conformations, with the "Tudor-ON" open form weakening its multimerization, while the "Tudor-OFF" closed form enhances multimerization via the YG-box (Fig. 4B). RNA binding at SMN's N-terminus may shift SMN from closed to open form, allowing Tudor domain interactions with sDMA-modified proteins to stabilize this conformation and trigger phase separation. At higher SMN concentrations, the closed form spontaneously reappears, facilitating multimerization-driven condensates. This model accounts for the separation of Gems from Cajal bodies during maturation. SMN's shift back to a closed form upon snRNP release might explain why snRNPs ultimately accumulate in Cajal bodies and Gem-associated SMN is snRNP-free [61]. This model further suggests that condensate formation through Tudor-sDMA interactions has the ability to sequester complexes containing sDMA proteins, such snRNPs, within the condensate—an ability that likely was not present in ancestral SMN. Tudor-sDMA interactions are an evolutionary "add-on" function of SMN; therefore, considering the function of other Tudor domain proteins can help to clarify the role of U-bodies.

5. Tudor Domain and sDMA, a Possible Unit for Cellular Short Memory

5.1 Most Tudor Domains Are Involved in piRNA Biogenesis

The Tudor domain is a conserved domain characterized by its phenylalanine residues, which form an aromatic cage structure that binds dimethylated arginine or methylated lysine. Although the human genome contains fifteen Tudor domain-containing proteins [76], many of these proteins are expressed in germ cells to assist in piRNA biogenesis. piRNA is a short RNA that contains sequences complementary to transposable elements [77,78]. Drosophila oocytes serve as a model system for piRNA production, revealing diverse pathways for piRNA generation. In follicle cells, piRNA is produced in Yb-bodies by processing RNA transcribed from piRNA clusters [78], while in germ cells, piwi family proteins digest transposon mRNA to generate piRNA. Three piwi proteins—Aub and AGO3— reciprocally cleave transposon mRNA in a process known as "the ping-pong cycle" in nuage, a germ cell-specific, membrane-less organelle that surrounds the nucleus [78]. In either pathway, the piRNA complexed with piwi protein recognizes transposable elements via complementarity to piRNA, silencing them by cleavage or transcription repression following nuclear import, thus protecting the genome from transposon.

5.2 Nuage in Immune Regulation and Autoimmunity Prevention

Piwi family proteins contain dimethylated arginine at their N-termini, and several Tudor domain proteins bind these dimethylated sites with specific affinity [76]. These interactions are essential for generating a diverse piRNA repertoire, which is necessary for preventing transposon mobilization. Given that Tudor domain-sDMA interactions can induce phase-separated condensates [73], these interactions likely contribute to the formation of nuage, a cytoplasmic granule for piRNA production. In mammalian male germ cells, TDRD1, a Tudor domain protein, is essential for forming phase-separated condensates via self-interactions through its C-terminal coiled-coil domain and interactions between its Tudor domain and sDMA in other proteins. These condensates function in the piRNA pathway and are critical for male fertility [79]. Recent studies highlight the importance of compartmentalizing piRNA-related granules for maintaining piRNA pathway fidelity. While Yb-bodies differ from nuage as they form through the phase separation of the IDR of Vasa/DDX4 protein [80], Yb, a component of Yb-bodies controls RNA substrate specificity for piRNA production by interacting with ATP-dependent RNA helicase Armi, which recognizes piRNA precursor [81]. When Yb is absent, or when mutant Armi lacks ATPase activity,

Armi binds promiscuous RNA, leading to the production of non-transposon targeting piRNA. This suggests that the piRNA-dependent immune system can turn against the genome itself in the absence of correct compartmentalization [81]. Comparative studies of closely related species indicate an evolutional trade-off between the efficiency of transposon sensing and autoimmunity prevention [82]. This emphasizes the importance of compartmentalization in ensuring piRNA system fidelity and avoiding deleterious autoimmune responses [83]. Thus, the addition of Tudor-sDMA interactions to SMN may be advantageous in avoiding crosstalk between snRNA biogenesis and other RNA processing machinery, particularly piRNA pathways in germ cells. This is consistent with the observation that U-bodies are constitutively formed in Drosophila oocytes. Indeed, nuage and U-bodies have been observed in the same Drosophila nurse cells, suggesting the necessity of separating these components into distinct compartments via different Tudor-DMA interactions [84]. In mouse dendritic cells, short RNAs (18-24 nucleotides) derived from snRNA have been identified, some of which are processed by Dicer, suggesting that snRNA might be treated as miRNA precursors [85]. Partitioning snRNA away from piRNA precursor into separate compartments may prevent misincorporation into the piRNA processing.

5.3 Arginine Methylation as a Short Memory to Discriminate Self and Non-self

For accurate discrimination between self and non-self molecules, Tudor-sDMA-mediated phase separation may be highly effective. A metabolomic analysis demonstrated that the turnover rate of arginine methylation is much slower than that of phosphorylation [86]. This slow turnover allows sDMA to function as a label, certifying that proteins have spent a significant amount of time in host cells, whereas acute viral proteins cannot acquire the label as rapidly. This mechanism likely enables cells to distinguish snRNA from viral RNA by decorating sDMA-modified Sm-ring. A similar principle has also been observed for RNA methylation at the first coding nucleotide of mRNA, forming Cap1 and Cap2, which marks cellular RNA as distinct from acute viral RNA, although in the case of snRNA, it may function as a degradation tag. The slower kinetics of methylation are also employed in bacterial chemotaxis adaptation as a short-time memory [87], highlighting the general use of methylation as a memory mechanism reflecting elapsed time. The addition of the Tudor-sDMA module to SMN would have allowed the cell to accumulate host components related to snRNP assembly in U-bodies, segregating from other RNA and proteins potentially derived from mobile elements and viruses. Additionally, U-bodies are often attached to P-bodies, likely through interactions with sDMA proteins [6], which could facilitate the transfer of defective snRNP components to P-bodies for degradation, preventing the innate immune system from mistakenly responding to these RNAs. Alternatively, the induction of U-bodies under stress conditions [7,8] may increase the sensitivity of the innate immune system to nascent U snRNA, such as RVU1-18, by sequestering the Gemin complex. Moreover, U-bodies could support RIG-I pathway activation as a signaling hub, similar to stress granules. In the next section, we will further discuss this topic, focusing on a recent study that uses Drosophila SMA models with mutations in the SMN gene.

6 Autoimmune Response and Spinal Muscular Atrophy

6.1 Innate Immune Response in SMA Disease Models

The potential for snRNA to activate the innate immune system suggests that defects in SMN or the Gemin complex could trigger inflammation. The fly Phax mutant, which is defective in snRNA export and causes splicing changes similar to the SMN mutant, did not show any transcriptional stress response as observed in the SMN mutant. This finding suggests that the immune reaction to snRNA may be mediated by the cytoplasmic sensor system [88]. Furthermore, a recent study of a Drosophila SMA model provided a detailed analysis of how reduced SMN levels activate the innate immune system [89]. SMN hypomorphic flies exhibited hyperactivation of innate immunity, revealed by proteomic and transcriptomic analyses, alongside an increase in

melanotic masses, a defense response to pathogens or tissue damage. The correlation between the number of melanotic masses and the severity of SMN mutations suggests that innate immune response occurs in the absence of infection. Importantly, this innate immune activation was derived from SMN-hypomorphic condition in hemocytes and the fat body, an immune organ in flies, but not in neurons and muscle cells, indicating that SMN is required to directly suppress spontaneous innate immune activation. Further genetic interaction studies by RNAi combining SMN with other innate immune-related genes showed that reduction of Gemin3, 4, 5 and dart5 (a Drosophila PRMT5 homolog) suppresses the innate immune response triggered by hypomorphic SMN. The Gemin3/4/5 complex captures snRNA upon its arrival in the cytoplasm via interactions with CBC and PHAX. Reduction of SMN causes a delay of SMN recruitment to the Gemin3/4/5 complex, which is essential to progress into further steps, and the accumulation of this first survey complex may result in presenting snRNA to the innate immune system. Additionally, Gemin3 and Gemin4 form a complex with Drosophila IMD [90], an adaptor protein inducing immune signaling, raising the possibility that the snRNA-Gemin 3/4/5 complex could actively play a role as an immune sensor. Consistently, in the absence of SMN, Gemin5 binds to Sm-deficient U1 snRNA, leading to its accumulation in P-body [39]. Furthermore, Gemin5 is also known as a translation modulator through its ability to bind the 5' cap structure and viral IRES, and it is cleaved by viral protease during foot-and-mouth disease virus infection [91,92], suggesting that Gemin5 also functions in survey cytoplasmic RNA beyond its role in snRNP biogenesis.
Considering that both sDMA modification of Sm proteins and U-body formation are absent in the dart5 mutant [6,93], the loss of SMN function causes the spontaneous deposition of sDMA-modified Sm proteins on RNA, which may further enhance the innate immune response. The SMN Tudor domain may mask these proteins, facilitating U-body assembly. These results suggest that SMN functions as both a chaperone and a quality control checkpoint for genuine snRNA. Therefore, SMN deficiency leads to disrupted RNA sorting and an aberrant innate immune response.

6.2 Systemic Inflammation in SMA Due to Innate Immune Response?

While the primary symptom of SMA is muscular atrophy resulting from lower motor neuron degeneration, the reduction of SMN can affect all cell types due to its role in snRNP assembly. Indeed, abnormalities in peripheral tissues have also been observed in SMA mouse models [94]. SMA mice with reduced SMN expression specifically in motor neurons exhibit milder disease phenotypes compared to models with ubiquitous SMN deficiency [94]. This suggests that SMN deficiency in peripheral tissues may contribute to disease progression. Systemic inflammation has been observed in SMA mouse models, partly due to bacterial translocation into the bloodstream caused by increased intestinal permeability [95]. However, systemic inflammation occurs in early stages of the disease, making it difficult to fully attribute this inflammation to gut permeability alone. Global gene expression analysis in the liver also revealed activation of innate immune responses, although inflammation could also be driven by secreted factors from damaged tissues or immune system dysfunction [95].
Recent analyses of serum and cerebrospinal fluid (CSF) from SMA patients have shown increased levels of pro-inflammatory cytokines, which were attenuated following Nusinersen treatment [96–98]. This suggests that reduced SMN levels may induce innate immune responses in various cell types. SMA mouse models also exhibited elevated pro-inflammatory cytokine levels in serum [99,100]. Neuroinflammation, resulting from excessive microglial activity during motor circuit development, has been implicated in the development of SMA motor neuron phenotypes [101]. In amyotrophic lateral sclerosis (ALS), another neuromuscular disease characterized by motor neuron degeneration, mutant genes associated with familial ALS cause cytoplasmic snRNA accumulation. For example, mutant FUS protein forms cytoplasmic complexes with U1 snRNA [102–104], while toxic dipeptide repeats from C9ORF72 induce U2 snRNP cytoplasmic translocation [105]. SMA and ALS share molecular hallmarks reflecting defects in snRNP

biogenesis, such as Gem depletion [106]. Further analysis investigating whether prolonged retention of these RNPs in the cytoplasm triggers innate immune activation would shed light on the neuroinflammation observed in ALS.

In this review, we have discussed the roles of U-bodies in preventing snRNA from being misrecognized by the innate immune system (Fig. 5) and focused on the molecular basis of SMN in regulating the assembly mechanism of U-bodies. Our hypothesis suggests that U-bodies function as part of a physiological mechanism to recognize and retain snRNA as self-RNA. Further studies into the roles of these condensates are needed, as they may pave the way for new therapeutic strategies targeting diseases caused by RNA metabolism abnormalities.

Acknowledgment
We thank Yuka Yoshida and other lab members for their assistance and valuable discussions. This study was supported by JSPS KAKENHI Grant Numbers 23K06093 (H.M.) and KAKENHI Grant-in-Aid for Transformative Research Areas 21H05274 (S.N.).

Declaration of generative AI in the writing process
During the preparation of this work, the authors used ChatGPT for English proofreading and to enhance readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Reference

[1] B. Van Treeck, R. Parker, Emerging roles for intermolecular RNA-RNA interactions in RNP assemblies, Cell 174 (2018) 791–802.
[2] W. Borcherds, A. Bremer, M.B. Borgia, T. Mittag, How do intrinsically disordered protein regions encode a driving force for liquid–liquid phase separation?, Curr. Opin. Struct. Biol. 67 (2021) 41–50.
[3] S.V. Nesterov, N.S. Ilyinsky, V.N. Uversky, Liquid-liquid phase separation as a common organizing principle of intracellular space and biomembranes providing dynamic adaptive responses, Biochim. Biophys. Acta Mol. Cell Res. 1868 (2021) 119102.
[4] H.J. Wiedner, J. Giudice, It's not just a phase: function and characteristics of RNA-binding proteins in phase separation, Nat. Struct. Mol. Biol. 28 (2021) 465–473.
[5] T. Hirose, K. Ninomiya, S. Nakagawa, T. Yamazaki, A guide to membraneless organelles and their various roles in gene regulation, Nat. Rev. Mol. Cell Biol. (2022). https://doi.org/10.1038/s41580-022-00558-8.
[6] J.-L. Liu, J.G. Gall, U bodies are cytoplasmic structures that contain uridine-rich small nuclear ribonucleoproteins and associate with P bodies, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 11655–11659.
[7] J. Tsalikis, I. Tattoli, A. Ling, M.T. Sorbara, D.O. Croitoru, D.J. Philpott, S.E. Girardin, Intracellular Bacterial Pathogens Trigger the Formation of U Small Nuclear RNA Bodies (U Bodies) through Metabolic Stress Induction, J. Biol. Chem. 290 (2015) 20904–20918.
[8] M. Buckingham, J.-L. Liu, U bodies respond to nutrient stress in Drosophila, Exp. Cell Res. 317 (2011) 2835–2844.
[9] C.L. Will, R. Lührmann, Spliceosome structure and function, Cold Spring Harb. Perspect. Biol. 3 (2011). https://doi.org/10.1101/cshperspect.a003707.

[10] R. Wan, R. Bai, X. Zhan, Y. Shi, How Is Precursor Messenger RNA Spliced by the Spliceosome?, Annu. Rev. Biochem. 89 (2020) 333–358.
[11] M.E. Wilkinson, C. Charenton, K. Nagai, RNA Splicing by the Spliceosome, Annu. Rev. Biochem. 89 (2020) 359–388.
[12] M.K. Sakharkar, V.T. Chow, P. Kangueane, Distributions of exons and introns in the human genome, In Silico Biology 4 (2004) 387–393.
[13] R.J. Cauchi, SMN and Gemins: "we are family" … or are we?: insights into the partnership between Gemins and the spinal muscular atrophy disease protein SMN: Insights into the partnership between Gemins and the spinal muscular atrophy disease protein SMN, Bioessays 32 (2010) 1077–1089.
[14] U. Fischer, C. Englbrecht, A. Chari, Biogenesis of spliceosomal small nuclear ribonucleoproteins: Biogenesis of spliceosomal snRNPs, Wiley Interdiscip. Rev. RNA 2 (2011) 718–731.
[15] G. Matera, Z. Wang, A day in the life of the spliceosome, Nat. Rev. Mol. Cell Biol. 15 (2014) 108–121.
[16] J. Mouaikel, C. Verheggen, E. Bertrand, J. Tazi, R. Bordonné, Hypermethylation of the cap structure of both yeast snRNAs and snoRNAs requires a conserved methyltransferase that is localized to the nucleolus, Mol. Cell 9 (2002) 891–901.
[17] D. Becker, A.G. Hirsch, L. Bender, T. Lingner, G. Salinas, H. Krebber, Nuclear pre-snRNA export is an essential quality assurance mechanism for functional spliceosomes, Cell Rep. 27 (2019) 3199-3214.e3.
[18] U.T. Meier, RNA modification in Cajal bodies, RNA Biol. 14 (2017) 693–700.
[19] P. Morais, H. Adachi, Y.-T. Yu, Spliceosomal snRNA Epitranscriptomics, Front. Genet. 12 (2021) 652129.
[20] M.T. Bohnsack, K.E. Sloan, Modifications in small nuclear RNAs and their roles in spliceosome assembly and function, Biol. Chem. 399 (2018) 1265–1276.
[21] T. Ma, E.S. Xiong, R.M. Lardelli, J. Lykke-Andersen, Sm complex assembly and 5′ cap trimethylation promote selective processing of snRNAs by the 3′ exonuclease TOE1, Proc. Natl. Acad. Sci. U.S.A. 121 (2024). https://doi.org/10.1073/pnas.2315259121.
[22] M. Ohno, A. Segref, A. Bachi, M. Wilm, I.W. Mattaj, PHAX, a mediator of U snRNA nuclear export whose activity is regulated by phosphorylation, Cell 101 (2000) 187–198.
[23] A. McCloskey, I. Taniguchi, K. Shinmyozu, M. Ohno, hnRNP C tetramer measures RNA length to classify RNA polymerase II transcripts for export, Science 335 (2012) 1643–1646.
[24] S. Kitao, A. Segref, J. Kast, M. Wilm, I.W. Mattaj, M. Ohno, A compartmentalized phosphorylation/dephosphorylation system that regulates U snRNA export from the nucleus, Mol. Cell. Biol. 28 (2008) 487–497.
[25] E. Martinez-Salas, A. Embarc-Buh, R. Francisco-Velilla, Emerging Roles of Gemin5: From snRNPs Assembly to Translation Control, Int. J. Mol. Sci. 21 (2020). https://doi.org/10.3390/ijms21113868.
[26] Y. Dou, S. Kalmykova, M. Pashkova, M. Oghbaie, H. Jiang, K.R. Molloy, B.T. Chait, M.P. Rout, D. Fenyö, T.H. Jensen, I. Altukhov, J. LaCava, Affinity proteomic dissection of the human nuclear cap-binding complex interactome, Nucleic Acids Res. 48 (2020) 10456–10469.
[27] H. Ishikawa, Y. Nobe, K. Izumikawa, H. Yoshikawa, N. Miyazawa, G. Terukina, N.

Kurokawa, M. Taoka, Y. Yamauchi, H. Nakayama, T. Isobe, N. Takahashi, Identification of truncated forms of U1 snRNA reveals a novel RNA degradation pathway during snRNP biogenesis, Nucleic Acids Res. 42 (2014) 2708–2724.
[28] W.J. Friesen, S. Paushkin, A. Wyce, S. Massenet, G.S. Pesiridis, G. Van Duyne, J. Rappsilber, M. Mann, G. Dreyfuss, The methylosome, a 20S complex containing JBP1 and pICln, produces dimethylarginine-modified Sm proteins, Mol. Cell. Biol. 21 (2001) 8289–8300.
[29] E. Paknia, A. Chari, H. Stark, U. Fischer, The ribosome cooperates with the assembly chaperone pICln to initiate formation of snRNPs, Cell Rep. 16 (2016) 3103–3112.
[30] C. Grimm, A. Chari, J.-P. Pelz, J. Kuper, C. Kisker, K. Diederichs, H. Stark, H. Schindelin, U. Fischer, Structural basis of assembly chaperone- mediated snRNP formation, Mol. Cell 49 (2013) 692–703.
[31] N. Neuenkirchen, C. Englbrecht, J. Ohmer, T. Ziegenhals, A. Chari, U. Fischer, Reconstitution of the human U snRNP assembly machinery reveals stepwise Sm protein organization, EMBO J. 34 (2015) 1925–1941.
[32] R. Zhang, B.R. So, P. Li, J. Yong, T. Glisovic, L. Wan, G. Dreyfuss, Structure of a key intermediate of the SMN complex reveals Gemin2's crucial function in snRNP assembly, Cell 146 (2011) 384–395.
[33] D.G. Scofield, M. Lynch, Evolutionary diversification of the Sm family of RNA-associated proteins, Mol. Biol. Evol. 25 (2008) 2255–2267.
[34] V. Despic, S.R. Jaffrey, mRNA ageing shapes the Cap2 methylome in mammalian mRNA, Nature 614 (2023) 358–366.
[35] S. Shukla, R. Parker, Quality control of assembly-defective U1 snRNAs by decapping and 5'-to-3' exonucleolytic digestion, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E3277-86.
[36] A. Roithová, Z. Feketová, Š. Vaňáčová, D. Staněk, DIS3L2 and LSm proteins are involved in the surveillance of Sm ring-deficient snRNAs, Nucleic Acids Res. 48 (2020) 6184–6197.
[37] R.M. Lardelli, J. Lykke-Andersen, Competition between maturation and degradation drives human snRNA 3' end quality control, Genes Dev. 34 (2020) 989–1001.
[38] A.B. Prusty, R. Meduri, B.K. Prusty, J. Vanselow, A. Schlosser, U. Fischer, Impaired spliceosomal UsnRNP assembly leads to Sm mRNA down-regulation and Sm protein degradation, J. Cell Biol. 216 (2017) 2391–2407.
[39] D. Jiang, X. Zou, C. Zhang, J. Chen, Z. Li, Y. Wang, Z. Deng, L. Wang, S. Chen, Gemin5 plays a role in unassembled ‐ U1 sn RNA disposal in SMN ‐ deficient cells, FEBS Letters 592 (2018) 1400−1411.
[40] R.M. Borg, R. Bordonne, N. Vassallo, R.J. Cauchi, Genetic interactions between the members of the SMN-Gemins complex in Drosophila, PLoS One 10 (2015) e0130974.
[41] R.M. Borg, B. Fenech Salerno, N. Vassallo, R. Bordonne, R.J. Cauchi, Disruption of snRNP biogenesis factors Tgs1 and pICln induces phenotypes that mirror aspects of SMN-Gemins complex perturbation in Drosophila, providing new insights into spinal muscular atrophy, Neurobiol. Dis. 94 (2016) 245–258.
[42] K. Schmitz, J. Cox, L.M. Esser, M. Voss, K. Sander, A. Löffler, F. Hillebrand, S. Erkelenz, H. Schaal, T. Kähne, S. Klinker, T. Zhang, L. Nagel-Steger, D. Willbold, S. Seggewiß, D. Schlütermann, B. Stork, M. Grimmler, S. Wesselborg, C. Peter, An

essential role of the autophagy activating kinase ULK1 in snRNP biogenesis, Nucleic Acids Res. 49 (2021) 6437–6455.
[43] J. Yong, L. Wan, G. Dreyfuss, Why do cells need an assembly machine for RNA–protein complexes?, Trends Cell Biol. 14 (2004) 226–232.
[44] G. Liu, M.U. Gack, Distinct and orchestrated functions of RNA sensors in innate immunity, Immunity 53 (2020) 26–42.
[45] G.A. Corbet, J.M. Burke, R. Parker, Nucleic acid-protein condensates in innate immune signaling, EMBO J. 42 (2023) e111870.
[46] W. Martin, E.V. Koonin, Introns and the origin of nucleus-cytosol compartmentalization, Nature 440 (2006) 41–45.
[47] D.B. Haack, N. Toor, Retroelement origins of pre-mRNA splicing, Wiley Interdiscip. Rev. RNA 11 (2020) e1589.
[48] S. Valadkhan, A. Mohammadi, Y. Jaladat, S. Geisler, Protein-free small nuclear RNAs catalyze a two-step splicing reaction, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 11901–11906.
[49] M. Marcia, A.M. Pyle, Visualizing group II intron catalysis through the stages of splicing, Cell 151 (2012) 497–507.
[50] S.M. Fica, M.A. Mefford, J.A. Piccirilli, J.P. Staley, Evidence for a group II intron-like catalytic triplex in the spliceosome, Nat. Struct. Mol. Biol. 21 (2014) 464–471.
[51] L. Zhang, A. Vielle, S. Espinosa, R. Zhao, RNAs in the spliceosome: Insight from cryoEM structures, Wiley Interdiscip. Rev. RNA 10 (2019) e1523.
[52] D.R.E. Ranoa, A.D. Parekh, S.P. Pitroda, X. Huang, T. Darga, A.C. Wong, L. Huang, J. Andrade, J.P. Staley, T. Satoh, S. Akira, R.R. Weichselbaum, N.N. Khodarev, Cancer therapies activate RIG-I-like receptor pathway through endogenous non-coding RNAs, Oncotarget 7 (2016) 26496–26515.
[53] F. Zhang, S. Liu, Z. Qiao, L. Li, Y. Han, J. Sun, C. Ge, J. Zhu, D. Li, H. Yao, H. Zhang, J. Dai, Y. Yan, Z. Chen, L. Yin, F. Ma, Housekeeping U1 snRNA facilitates antiviral innate immunity by promoting TRIM25-mediated RIG-I activation, Cell Rep. 43 (2024) 113945.
[54] G. Stepanov, E. Zhuravlev, V. Shender, A. Nushtaeva, E. Balakhonova, E. Mozhaeva, M. Kasakin, V. Koval, A. Lomzov, M. Pavlyukov, I. Malyants, M. Zhorov, T. Kabilova, E. Chernolovskaya, V. Govorun, E. Kuligina, D. Semenov, V. Richter, Nucleotide modifications decrease innate immune response induced by synthetic analogs of snRNAs and snoRNAs, Genes (Basel) 9 (2018) 531.
[55] E. Stejskalová, D. Staněk, The splicing factor U1-70K interacts with the SMN complex and is required for nuclear gem integrity, J. Cell Sci. 127 (2014) 3909–3915.
[56] R.J. Cauchi, Gem formation upon constitutive Gemin3 overexpression in Drosophila, Cell Biol. Int. 35 (2011) 1233–1238.
[57] G.B. Gonsalvez, G.B. Gonsalvez, K. Praveen, K. Praveen, A.J. Hicks, A.J. Hicks, L. Tian, A. Matera, Sm protein methylation is dispensable for snRNP assembly in Drosophila melanogaster, RNA 14 (2008) 878–887.
[58] L. Lee, S.E. Davies, J.-L. Liu, The spinal muscular atrophy protein SMN affects Drosophila germline nuclear organization through the U body–P body pathway, Dev. Biol. 332 (2009) 142–155.
[59] R.J. Cauchi, L. Sanchez-Pulido, J.-L. Liu, Drosophila SMN complex proteins Gemin2, Gemin3, and Gemin5 are components of U bodies, Exp. Cell Res. 316 (2010) 2354–2364.

[60] L. Pellizzoni, N. Kataoka, B. Charroux, G. Dreyfuss, A novel function for SMN, the spinal muscular atrophy disease gene product, in pre-mRNA splicing, Cell 95 (1998) 615–624.
[61] S. Ohazama, A. Fujimoto, D. Konda, R. Yokoyama, S. Nakagawa, H. Maita, Dissecting the role of SMN multimerization in its dissociation from the Cajal body using harmine as a tool compound, J. Cell Sci. 137 (2024) jcs261834.
[62] M.S. Weiss, K. Diederichs, R.J. Read, S. Panjikar, G.D. Van Duyne, A.G. Matera, U. Fischer, C. Grimm, A critical examination of the recently reported crystal structures of the human SMN protein, Hum. Mol. Genet. 25 (2016) 4717–4725.
[63] M. Varadi, S. Anyango, M. Deshpande, S. Nair, C. Natassia, G. Yordanova, D. Yuan, O. Stroe, G. Wood, A. Laydon, A. Žídek, T. Green, K. Tunyasuvunakool, S. Petersen, J. Jumper, E. Clancy, R. Green, A. Vora, M. Lutfi, M. Figurnov, A. Cowie, N. Hobbs, P. Kohli, G. Kleywegt, E. Birney, D. Hassabis, S. Velankar, AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models, Nucleic Acids Res. 50 (2022) D439–D444.
[64] D. Piovesan, A.M. Monzon, S.C.E. Tosatto, Intrinsic protein disorder and conditional folding in AlphaFoldDB, Protein Sci. 31 (2022) e4466.
[65] T.R. Alderson, I. Pritišanac, Đ. Kolarić, A.M. Moses, J.D. Forman-Kay, Systematic identification of conditionally folded intrinsically disordered regions by AlphaFold2, Proc. Natl. Acad. Sci. U. S. A. 120 (2023) e2304302120.
[66] R. Martin, K. Gupta, N.S. Ninan, K. Perry, G.D. Van Duyne, The survival motor neuron protein forms soluble glycine zipper oligomers, Structure 20 (2012) 1929–1939.
[67] K. Gupta, R. Martin, R. Sharp, K.L. Sarachan, Oligomeric properties of survival motor neuron· Gemin2 complexes, Journal of Biological (2015). https://www.jbc.org/article/S0021-9258(20)42158-1/abstract.
[68] K. Gupta, Y. Wen, N.S. Ninan, A.C. Raimer, R. Sharp, A.M. Spring, K.L. Sarachan, M.C. Johnson, G.D. Van Duyne, A.G. Matera, Assembly of higher-order SMN oligomers is essential for metazoan viability and requires an exposed structural motif present in the YG zipper dimer, Nucleic Acids Res. 49 (2021) 7644–7664.
[69] C.L. Lorson, E.J. Androphy, The domain encoded by exon 2 of the survival motor neuron protein mediates nucleic acid binding, Hum. Mol. Genet. 7 (1998) 1269–1275.
[70] S. Bertrandy, P. Burlet, O. Clermont, C. Huber, C. Fondrat, D. Thierry-Mieg, A. Munnich, S. Lefebvre, The RNA-binding properties of SMN: deletion analysis of the zebrafish orthologue defines domains conserved in evolution, Hum. Mol. Genet. 8 (1999) 775–782.
[71] P.J. Young, N.T. Man, C.L. Lorson, T.T. Le, E.J. Androphy, A.H. Burghes, G.E. Morris, The exon 2b region of the spinal muscular atrophy protein, SMN, is involved in self-association and SIP1 binding, Hum. Mol. Genet. 9 (2000) 2869–2877.
[72] A.H.M. Burghes, C.E. Beattie, Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick?, Nat. Rev. Neurosci. 10 (2009) 597–609.
[73] E.M. Courchaine, A.E.S. Barentine, K. Straube, D.-R. Lee, J. Bewersdorf, K.M. Neugebauer, DMA-tudor interaction modules control the specificity of in vivo condensates, Cell 184 (2021) 3612-3625.e17.

[74] A.C. Raimer, K.M. Gray, A.G. Matera, SMN - A chaperone for nuclear RNP social occasions?, RNA Biol. 14 (2017) 701–711.
[75] Y. Hu, Y. Hou, S. Zhou, Y. Wang, C. Shen, L. Mu, D. Su, R. Zhang, Mechanism of assembly of snRNP cores assisted by ICln and the SMN complex in fission yeast, IScience 26 (2023) 107604.
[76] C. Chen, T.J. Nott, J. Jin, T. Pawson, Deciphering arginine methylation: Tudor tells the tale, Nat. Rev. Mol. Cell Biol. 12 (2011) 629–642.
[77] B. Czech, M. Munafò, F. Ciabrelli, E.L. Eastwood, M.H. Fabry, E. Kneuss, G.J. Hannon, PiRNA-guided genome defense: From biogenesis to silencing, Annu. Rev. Genet. 52 (2018) 131–157.
[78] D.M. Ozata, I. Gainetdinov, A. Zoch, D. O'Carroll, P.D. Zamore, PIWI-interacting RNAs: small RNAs with big functions, Nat. Rev. Genet. 20 (2019) 89–108.
[79] J. Gao, J. Jing, G. Shang, C. Chen, M. Duan, W. Yu, K. Wang, J. Luo, M. Song, K. Chen, C. Chen, T. Zhang, D. Ding, TDRD1 phase separation drives intermitochondrial cement assembly to promote piRNA biogenesis and fertility, Dev. Cell (2024). https://doi.org/10.1016/j.devcel.2024.06.017.
[80] T.J. Nott, E. Petsalaki, P. Farber, D. Jervis, E. Fussner, A. Plochowietz, T.D. Craggs, D.P. Bazett-Jones, T. Pawson, J.D. Forman-Kay, A.J. Baldwin, Phase transition of a disordered nuage protein generates environmentally responsive membraneless organelles, Mol. Cell 57 (2015) 936–947.
[81] H. Ishizu, T. Kinoshita, S. Hirakata, C. Komatsuzaki, M.C. Siomi, Distinct and collaborative functions of Yb and Armitage in transposon-targeting piRNA biogenesis, Cell Rep. 27 (2019) 1822-1835.e8.
[82] L. Wang, D.A. Barbash, E.S. Kelleher, Adaptive evolution among cytoplasmic piRNA proteins leads to decreased genomic auto-immunity, PLoS Genet. 16 (2020) e1008861.
[83] P.Y. Chung, K. Shoji, N. Izumi, Y. Tomari, Dynamic subcellular compartmentalization ensures fidelity of piRNA biogenesis in silkworms, EMBO Rep. 22 (2021) e51342.
[84] M.K. Jaglarz, M. Kloc, W. Jankowska, B. Szymanska, S.M. Bilinski, Nuage morphogenesis becomes more complex: two translocation pathways and two forms of nuage coexist in Drosophila germline syncytia, Cell Tissue Res. 344 (2011) 169–181.
[85] Y. Shi, Q. Shi, Q. Shen, Q. Zhang, X. Cao, Dicer-independent snRNA/snoRNA-derived nuclear RNA 3 regulates tumor-associated macrophage function by epigenetically repressing inducible nitric oxide synthase transcription, Cancer Commun. (Lond.) 41 (2021) 140–153.
[86] F. Zhang, J. Kerbl-Knapp, M.J. Rodriguez Colman, A. Meinitzer, T. Macher, N. Vujić, S. Fasching, E. Jany-Luig, M. Korbelius, K.B. Kuentzel, M. Mack, A. Akhmetshina, A. Pirchheim, M. Paar, B. Rinner, G. Hörl, E. Steyrer, U. Stelzl, B. Burgering, T. Eisenberg, B. Pertschy, D. Kratky, T. Madl, Global analysis of protein arginine methylation, Cell Rep. Methods 1 (2021) 100016.
[87] R. Colin, V. Sourjik, Emergent properties of bacterial chemotaxis pathway, Curr. Opin. Microbiol. 39 (2017) 24–33.
[88] E.L. Garcia, Y. Wen, K. Praveen, A.G. Matera, Transcriptomic comparison of Drosophila snRNP biogenesis mutants reveals mutant-specific changes in pre-mRNA processing: implications for spinal muscular atrophy, RNA 22 (2016) 1215–

1227.
[89] E.L. Garcia, R.E. Steiner, A.C. Raimer, L.E. Herring, A.G. Matera, A.M. Spring, Dysregulation of innate immune signaling in animal models of spinal muscular atrophy, BMC Biol. 22 (2024) 94.
[90] K.G. Guruharsha, J.-F. Rual, B. Zhai, J. Mintseris, P. Vaidya, N. Vaidya, C. Beekman, C. Wong, D.Y. Rhee, O. Cenaj, E. McKillip, S. Shah, M. Stapleton, K.H. Wan, C. Yu, B. Parsa, J.W. Carlson, X. Chen, B. Kapadia, K. VijayRaghavan, S.P. Gygi, S.E. Celniker, R.A. Obar, S. Artavanis-Tsakonas, A protein complex network of Drosophila melanogaster, Cell 147 (2011) 690–703.
[91] D. Piñeiro, J. Fernández-Chamorro, R. Francisco-Velilla, E. Martínez-Salas, Gemin5: A multitasking RNA-binding protein involved in translation control, Biomolecules 5 (2015) 528–544.
[92] M. Saiz, E. Martinez-Salas, Uncovering targets of the Leader protease: Linking RNA-mediated pathways and antiviral defense, Wiley Interdiscip. Rev. RNA 12 (2021) e1645.
[93] G.B. Gonsalvez, T.K. Rajendra, L. Tian, A.G. Matera, The Sm-protein methyltransferase, dart5, is essential for germ-cell specification and maintenance, Curr. Biol. 16 (2006) 1077–1089.
[94] G.-H. Park, Y. Maeno-Hikichi, T. Awano, L.T. Landmesser, U.R. Monani, Reduced survival of motor neuron (SMN) protein in motor neuronal progenitors functions cell autonomously to cause spinal muscular atrophy in model mice expressing the human centromeric (SMN2) gene, J. Neurosci. 30 (2010) 12005–12019.
[95] B. Wan, P. Feng, Z. Guan, L. Sheng, Z. Liu, Y. Hua, A severe mouse model of spinal muscular atrophy develops early systemic inflammation, Hum. Mol. Genet. 27 (2018) 4061–4076.
[96] S. Bonanno, P. Cavalcante, E. Salvi, E. Giagnorio, C. Malacarne, M. Cattaneo, F. Andreetta, A. Venerando, V. Pensato, C. Gellera, R. Zanin, M.T. Arnoldi, C. Dosi, R. Mantegazza, R. Masson, L. Maggi, S. Marcuzzo, Identification of a cytokine profile in serum and cerebrospinal fluid of pediatric and adult spinal muscular atrophy patients and its modulation upon nusinersen treatment, Front. Cell. Neurosci. 16 (2022). https://doi.org/10.3389/fncel.2022.98276010.3389/fncel.2022.982760.s001.
[97] T. Nuzzo, R. Russo, F. Errico, A. D'Amico, A.G. Tewelde, M. Valletta, A. Hassan, M. Tosi, C. Panicucci, C. Bruno, E. Bertini, A. Chambery, L. Pellizzoni, A. Usiello, Nusinersen mitigates neuroinflammation in severe spinal muscular atrophy patients, Commun. Med. (Lond.) 3 (2023) 28.
[98] X. Cheng, Y.-N. Li, Y.-B. Fan, H.-H. Zhao, L. Li, C. Lu, L.-H. Zhu, Q. Niu, Cytokines in cerebrospinal fluid as a prognostic predictor after treatment of nusinersen in SMA patients, Clin. Neurol. Neurosurg. 244 (2024) 108462.
[99] M.-O. Deguise, Y. De Repentigny, E. McFall, N. Auclair, S. Sad, R. Kothary, Immune dysregulation may contribute to disease pathogenesis in spinal muscular atrophy mice, Hum. Mol. Genet. 26 (2017) 801–819.
[100] M.-T. Khairallah, J. Astroski, S.K. Custer, E.J. Androphy, C.L. Franklin, C.L. Lorson, SMN deficiency negatively impacts red pulp macrophages and spleen development in mouse models of spinal muscular atrophy, Hum. Mol. Genet. 26 (2017) 932–941.
[101] A. Vukojicic, N. Delestrée, E.V. Fletcher, J.G. Pagiazitis, S. Sankaranarayanan, T.A. Yednock, B.A. Barres, G.Z. Mentis, The classical complement pathway

mediates microglia-dependent remodeling of spinal motor circuits during development and in SMA, Cell Rep. 29 (2019) 3087-3100.e7.
[102] Y. Yu, B. Chi, W. Xia, J. Gangopadhyay, T. Yamazaki, M.E. Winkelbauer-Hurt, S. Yin, Y. Eliasse, E. Adams, C.E. Shaw, R. Reed, U1 snRNP is mislocalized in ALS patient fibroblasts bearing NLS mutations in FUS and is required for motor neuron outgrowth in zebrafish, Nucleic Acids Res. 43 (2015) 3208–3218.
[103] S. Sun, S.-C. Ling, J. Qiu, C.P. Albuquerque, Y. Zhou, S. Tokunaga, H. Li, H. Qiu, A. Bui, G.W. Yeo, E.J. Huang, K. Eggan, H. Zhou, X.-D. Fu, C. Lagier-Tourenne, D.W. Cleveland, ALS-causative mutations in FUS/TLS confer gain and loss of function by altered association with SMN and U1-snRNP, Nat. Commun. 6 (2015) 6171.
[104] D. Jutzi, S. Campagne, R. Schmidt, S. Reber, J. Mechtersheimer, F. Gypas, C. Schweingruber, M. Colombo, C. von Schroetter, F.E. Loughlin, A. Devoy, E. Hedlund, M. Zavolan, F.H.-T. Allain, M.-D. Ruepp, Aberrant interaction of FUS with the U1 snRNA provides a molecular mechanism of FUS induced amyotrophic lateral sclerosis, Nat. Commun. 11 (2020) 6341.
[105] S. Yin, R. Lopez-Gonzalez, R.C. Kunz, J. Gangopadhyay, C. Borufka, S.P. Gygi, F.-B. Gao, R. Reed, Evidence that C9ORF72 dipeptide repeat proteins associate with U2 snRNP to cause mis-splicing in ALS/FTD patients, Cell Rep. 19 (2017) 2244–2256.
[106] R.J. Cauchi, Gem depletion: amyotrophic lateral sclerosis and spinal muscular atrophy crossover, CNS Neurosci. Ther. 20 (2014) 574–581.

Figure Legends

Figure 1
Top: In contrast to Cajal body formation, U-body formation is condition-dependent. In mammalian cells, nutrient stress and bacterial infection both suppress translation initiation, which leads to U-body formation. The mechanism by which the suppression of translation initiation affects snRNP biogenesis remains unclear. Bottom: Images of U-bodies. U-bodies induced in HeLa cells by thapsigargin treatment were visualized using an anti-SMN antibody (left). Simultaneously, DDX6, a marker of P-bodies, was observed using an anti-DDX6 antibody (middle). U-bodies were detected in a subset of cells (indicated by arrowheads), whereas P-bodies were present in all cells. A magnified view of the cell outlined in the yellow box shows merged signals from SMN (green) and DDX6 (magenta) (right). Green foci in the nucleus indicate Cajal bodies/Gems, while white foci represent cytoplasmic U-bodies. Notably, the number of P-bodies is significantly higher than that of U-bodies, and all U-bodies are associated with P-bodies.

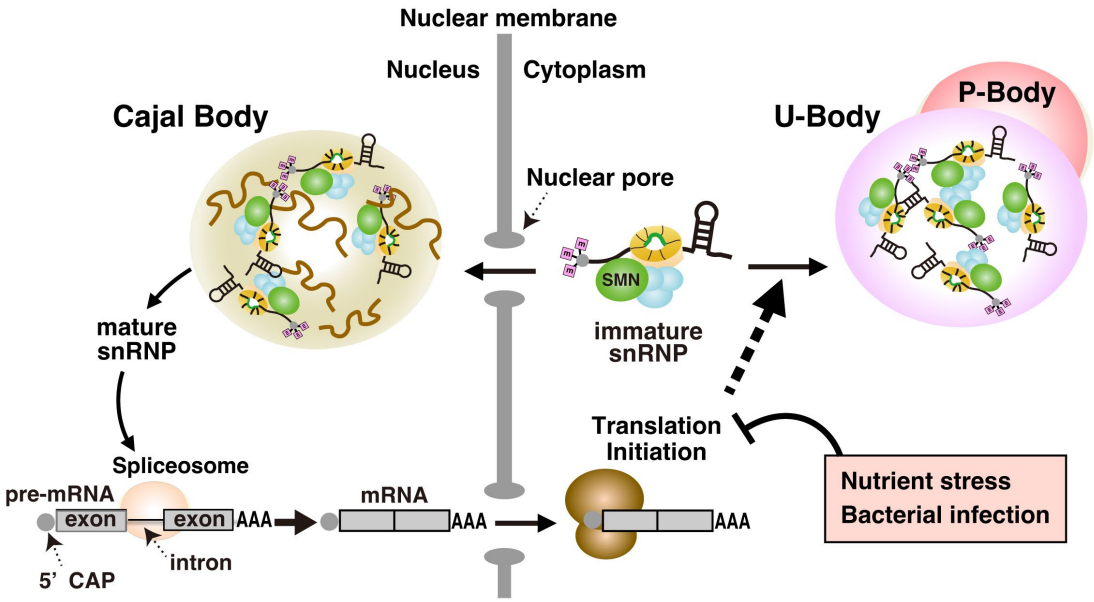
Figure 2
Overview of snRNP biogenesis. Nascent snRNA is transported to the cytoplasm, where it acquires an Sm ring and undergoes hypermethylation on its 5' cap structure, resulting in a partially mature snRNP. This complex is then imported into the nucleus, likely with SMN and part of the Gemin complex. Nuclear imported snRNPs are further modified in the Cajal body, and fully matured snRNPs exit the structure to assemble the spliceosome. The cytoplasmic processing steps are highlighted with a box, and further details are provided in Figure 3.

Figure 3
Both snRNA and Sm proteins are strictly regulated throughout their biogenesis pathway. Chaperone proteins continuously associate with these molecules, guiding them through each sequential step.

Figure 4
(A) Schematic structure of human SMN protein. Annotated domains are indicated as colored boxes. The structure predicted by Alphafold (AF-Q16637-F1) is shown with colors indicating each domain. The Tudor domain is magnified on the right to indicate the binding position of sDMA. (B) A model for the molecular behavior of SMN. Intrinsically disordered regions (IDRs) flanking the Tudor domain accommodate two states: a closed form that abrogates sDMA interactions of the Tudor domain and an open form stabilized by RNA and sDMA interactions. SMN in the open form contributes to the formation of phase-separated droplets, such as the Cajal body and U-body, while the closed form tends to oligomerize, leading to physically distinct condensates, such as Gem. This oligomerization-dependent chaperone function may represent the original role of SMN, with the Tudor domain adding a novel regulatory function. (C) Hypothesis on thesepration of Gem from Cajal body. Concentrated SMN in the Cajal body may spontaneously dissociate from Coilin and oligomerize in the closed form, forming a larger condensate recognized as Gem.

Figure 5
A model for the physiological roles of the U-body. Excessive or defective snRNA in the cytoplasm can be detected by cytoplasmic RNA sensors, potentially triggering an innate immune response. Sequestration of these molecules in the U-body may prevent autoactivation of innate immune signaling. SMN-sDMA interactions trigger U-body formation, and defects in SMN function may lead to innate immune activation, resulting in inflammation in SMA

Figure 1


Nuclear membrane
Nucleus
Cytoplasm
Cajal Body
U-Body
P-Body
Nuclear pore
SMN
mature snRNP
immature snRNP
Translation Initiation
Nutrient stress
Bacterial infection
Spliceosome
pre-mRNA
exon
exon
AAA
mRNA
AAA
AAA
5' CAP
intron

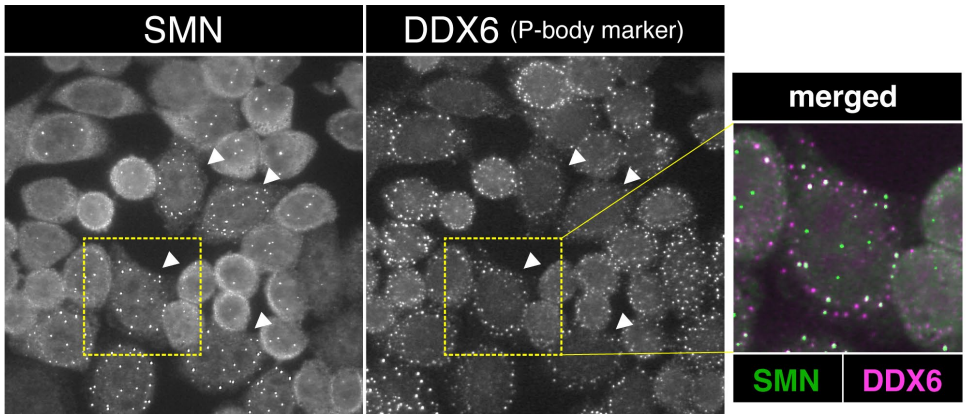

SMN
DDX6 (P-body marker)
merged
SMN
DDX6

Figure 2

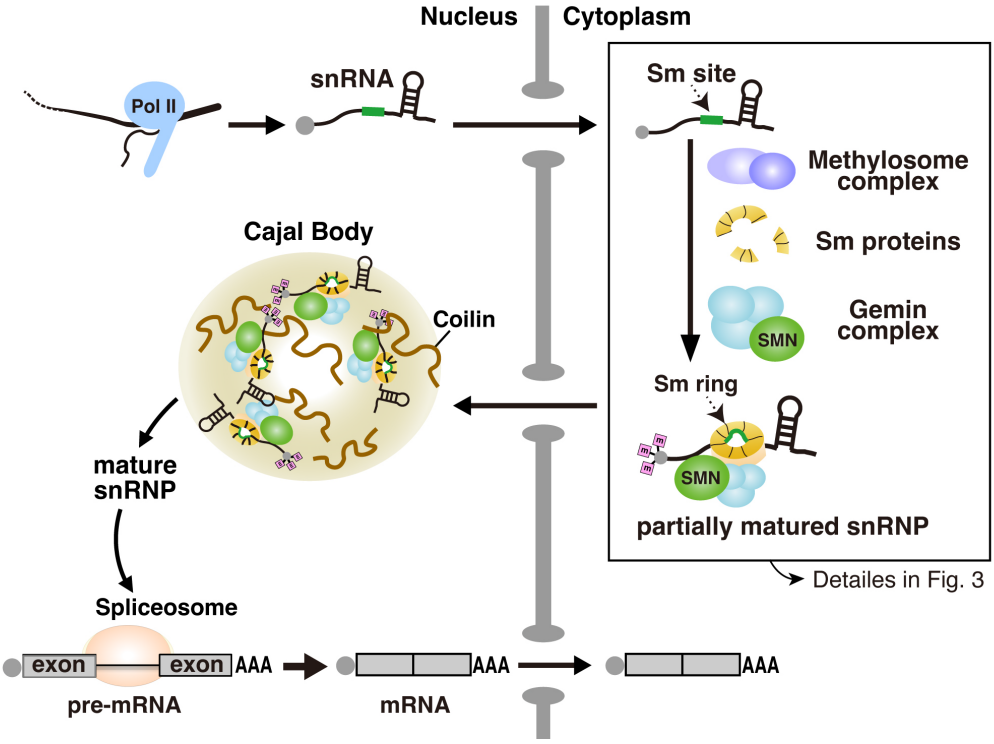

Nucleus
Cytoplasm
Pol II
snRNA
Sm site
Methylosome complex
Sm proteins
Gemin complex
SMN
Sm ring
SMN
partially matured snRNP
Detailes in Fig. 3
Cajal Body
Coilin
mature snRNP
Spliceosome
exon
exon
AAA
pre-mRNA
AAA
mRNA
AAA

Figure 3

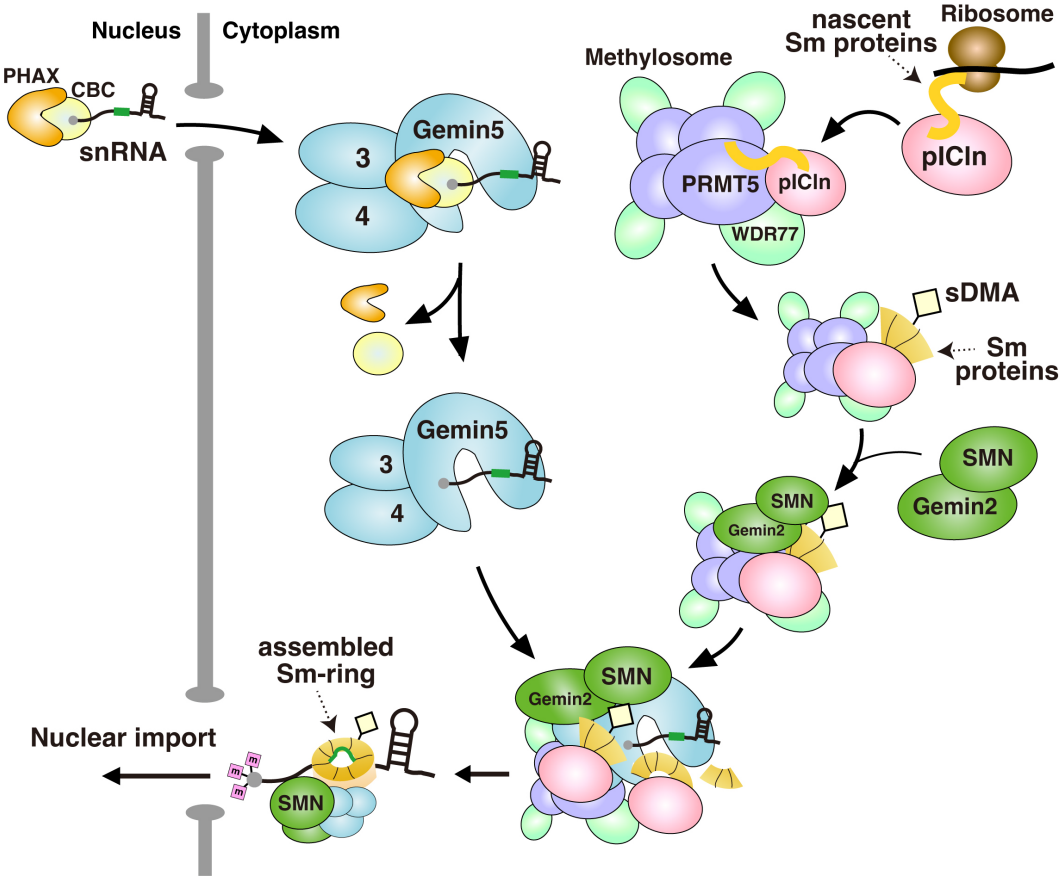

Nucleus
Cytoplasm
PHAX
CBC
snRNA
Gemin5
3
4
Methylosome
nascent
Sm proteins
Ribosome
pICln
PRMT5
pICln
WDR77
sDMA
Sm
proteins
SMN
Gemin2
assembled
Sm-ring
Nuclear import
m
m
m

Figure 4

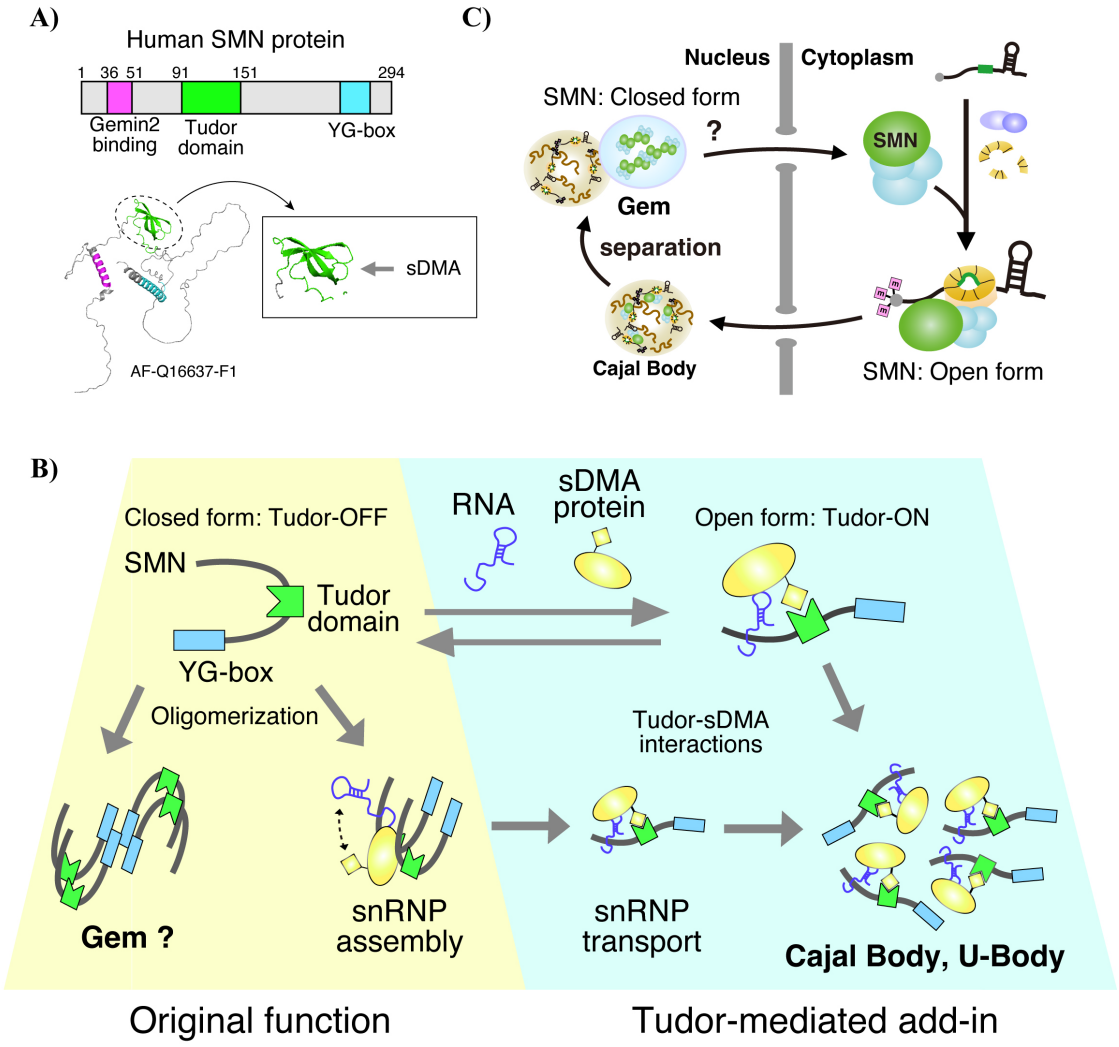
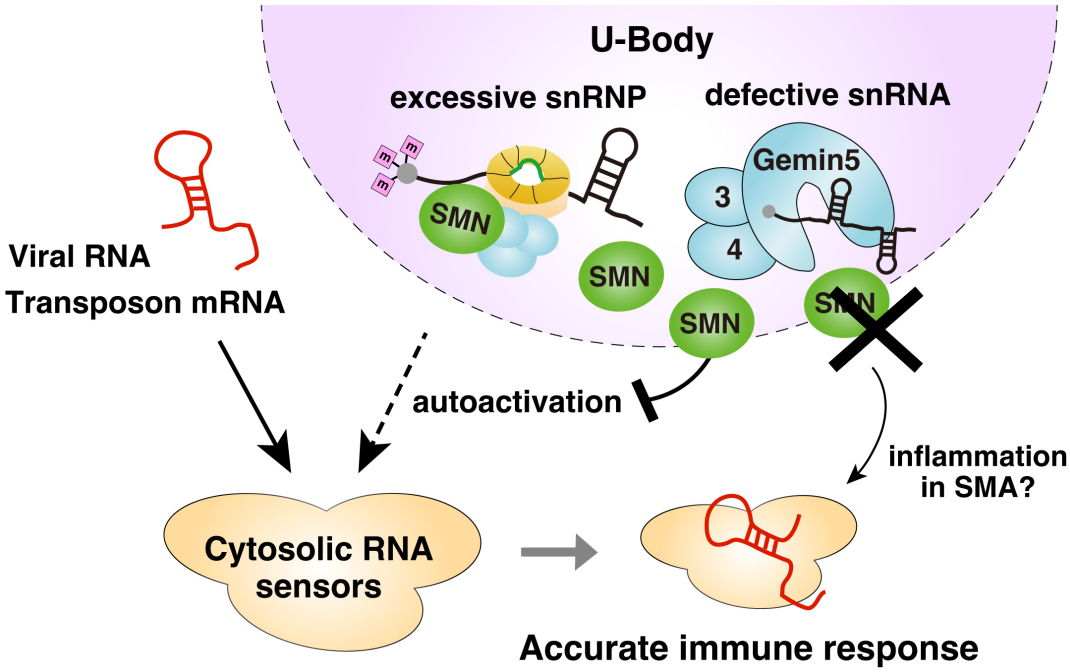

A)
Human SMN protein
1 36 51 91 151 294
Gemin2 binding
Tudor domain
YG-box
sDMA
AF-Q16637-F1
C)
Nucleus
Cytoplasm
SMN: Closed form
?
SMN
Gem
separation
Cajal Body
SMN: Open form
B)
Closed form: Tudor-OFF
SMN
Tudor domain
YG-box
Oligomerization
RNA
sDMA protein
Open form: Tudor-ON
Tudor-sDMA interactions
Gem ?
snRNP assembly
snRNP transport
Cajal Body, U-Body
Original function
Tudor-mediated add-in

Figure 5


U-Body
excessive snRNP
defective snRNA
SMN
SMN
SMN
SMN
Gemin5
3
4
Viral RNA
Transposon mRNA
autoactivation
inflammation
in SMA?
Cytosolic RNA
sensors
Accurate immune response