Biochemical Society Transactions (2024) **52** 465–479
https://doi.org/10.1042/BST20231116

PORTLAND PRESS

Review Article

The SMN-ribosome interplay: a new opportunity for Spinal Muscular Atrophy therapies

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The underlying cause of Spinal Muscular Atrophy (SMA) is in the reduction of survival motor neuron (SMN) protein levels due to mutations in the *SMN1* gene. The specific effects of SMN protein loss and the resulting pathological alterations are not fully understood. Given the crucial roles of the SMN protein in snRNP biogenesis and its interactions with ribosomes and translation-related proteins and mRNAs, a decrease in SMN levels below a specific threshold in SMA is expected to affect translational control of gene expression. This review covers both direct and indirect SMN interactions across various translation-related cellular compartments and processes, spanning from ribosome biogenesis to local translation and beyond. Additionally, it aims to outline deficiencies and alterations in translation observed in SMA models and patients, while also discussing the implications of the relationship between SMN protein and the translation machinery within the context of current and future therapies.

Introduction

Dysregulation of translation, either due to disturbance in ribosome biogenesis, tRNAs abundance, or pathways controlling translation initiation, and elongation, leads to various diseases [1], among which Spinal Muscular Atrophy (SMA) [2].

SMA is an autosomal recessive neurodegenerative disorder affecting lower motor neurons and, if left untreated, it is the first genetic cause of infant mortality [3]. SMA arises due to deletions or mutations in the *SMN1* (survival motor neuron) gene [4]. These mutations cause diminished levels of SMN protein [4], which are not fully compensated by the paralog *SMN2* gene. SMN plays fundamental roles in the biogenesis of ribonucleic particles [5–7], pre-mRNA splicing [8], and RNA metabolism at large [9]. In addition, SMN deficiency is likely linked to rDNA damage and impaired rRNA synthesis [10]. However, abnormalities in these functions observed in SMA cannot fully recapitulate the disease pathogenesis [11]. Expanding on preliminary observations about the connection between SMN and ribosomes [12–14], recent studies established the direct role of the SMN protein in translation as a ribosome-associated factor and the existence of translational defects in SMA [2,15–19]. This evidence underscores the role of SMN in orchestrating ribosome heterogeneity and offers a novel perspective on the molecular mechanism underpinning SMA pathology.

In this review, we discuss the role played by SMN in either directly or indirectly modulating the expression levels or activities of translation-related SMN interactors that are crucial to key biological processes and connections with SMA etiology [20]. We also provide a summary of evidence accumulated over the years highlighting translational alterations associated with SMA. These findings open a new scenario for the diagnostic and prognostic value of translational defects in specific mRNAs observed in SMA. For the development of translation-based therapies, it would be beneficial to strengthen the data linking SMA to translation. This information holds relevance not only for SMA but for other pathologies requiring a boost in translation. To facilitate the advancement of next-generation therapies for SMA, consolidating data that connects SMA with translation and elucidating

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Received: 22 December 2023
Revised: 12 February 2024
Accepted: 13 February 2024

Version of Record published: 23 February 2024

Biochemical Society Transactions (2024) 52 465–479
https://doi.org/10.1042/BST20231116

the mechanism through which SMN influences this cellular process would be advantageous. Specifically, further clarification is needed regarding whether SMN directly impacts translation initiation or elongation or both, and whether this influence is contingent upon the SMN complex.

SMN functions as a ribosome-associated protein, acting as a hub for translation

SMN is known for housekeeping contributions to the biogenesis of ribonucleoparticle complexes and to RNA splicing [9,21]. Numerous studies underlined the multifunctional nature of SMN, connecting the protein with axonal transport and outgrowth, mitochondrial activities, and proteostasis [20,22,23]. Increasing evidence shows that SMN is also closely related to protein synthesis through its association with the translational machinery and translation-related proteins and noncoding RNAs [2,12,13,17,24,25]. In this context, we will investigate various pieces of evidence suggesting that SMN establishes a platform within the ribosome for translation regulation of mRNAs associated with SMA pathogenesis.

A possible connection between the nuclear function of SMN and translation is through its well-characterized role in RNPs biogenesis and processing [9]. In the nucleus, SMN interacts with fibrillarin, a highly conserved nucleolar protein that is associated with Box C/D small nucleolar RNAs and exerts key functions in processing and post-transcriptional modification of rRNA [26]. Fibrillarin and SMN co-immunoprecipitate from nuclear extracts, indicating that the proteins are part of the same complex in cells [7,27]. In addition, in the nucleus, SMN interacts with nucleolin and protein B23 [28], known to associate with pre-rRNA particles and to play an essential role in transcribing ribosomal genes and pre-rRNA processing [29,30]. These results suggest that SMN might promote post-transcriptional modifications of rRNA that mediate both the structural organization of ribosomes and their function in controlling gene expression [26,31,32].

In the cytoplasm, evidence accrued over the last 10 years established the association of SMN with polysomes *in vitro* [2], in murine motoneuron-like cells [13,17,25], and in human fibroblasts [24]. SMN co-sediments with ribosomal proteins *in vivo* in mouse and rat spinal cords [2,12,17], and in mouse brain [2,17]. SMN also mediates the anchoring of ribosomes to the plasma membrane in human fibroblasts [33], controlling the local translation of mRNAs encoding ribosomal proteins [24]. Interestingly, SMN association with ribosomes and its components is RNA-independent, and tissue- and concentration-dependent [2].

Supporting these observations, multiple assays demonstrate that SMN protein directly interacts with components of the translation initiation complexes (such as eIF3 and eIF4G) or translation elongation factors (eEF1A) [14,25,34]. These interactions suggest that SMN plays a direct role in translation as shown *in vitro* and *in vivo* [2,13,17] in rodent and human fibroblasts [24,33]. In line with these findings, genuine SMN partners include ribosomal proteins from both the large and small ribosomal subunits, as observed in nuclear [35], cytoplasmic [14], and whole cell extract [36] (Table 1 and Figure 1). Supporting the putative interaction of SMN with both ribosomal subunits, co-sedimentation profiles of SMN from cell lines and multiple tissues [2,17] show that this is the case. These results anticipate the RNA-independent role of SMN as a ribosome-associated protein in mouse cell lines and tissues [2] and strengthen previous findings obtained with RIP-chip demonstrating that SMN binds rRNAs and tRNAs [44] (Table 2).

An intriguing link between the primary function of SMN in the formation of Gemin granules involved in snRNPs biogenesis [5–7], and its direct role in translation may be attributed to Gemin5. Recognized as an RNA-binding protein (RBP) [54], Gemin5 takes part in snRNP assembly [55,56], and additionally regulates translation by associating with ribosomes in polysomes [38,57] through mRNAs bearing specific RNA features [57]. These findings suggest that the interaction between Gemin5 and ribosomes is likely RNA-dependent, raising the possibility that SMN might mediate this interaction. Whilst mRNAs bound by SMN-primed ribosomes (i.e. ribosomes bound by SMN) are closely tied to processes disrupted in SMA [2,17], variants of Gemin5 interfere with a different set of transcripts and pathways [58]. These observations indicate the involvement of distinct molecular pathomechanisms and a complex interplay between SMN and Gemin5 with the translation machinery, warranting further investigation.

This observation, coupled with the notion that SMN expression levels vary in different tissues [22], suggests a tissue-specific and widespread regulation of mRNA translation, as observed in the case of the *RPS6* mRNA [24]. The direct role of SMN-primed ribosomes in the translational control of a subset of mRNAs was investigated using selective ribosome profiling [2]. Selective ribosome profiling showed that SMN-primed ribosomes primarily bind the beginning of the coding sequence of around 600 mRNAs in the mouse brain (i.e.

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Table 1. Translation-related protein partners of SMN

		Assay					
		Homo sapiens					*Rattus norvegicus*
Translation component	**Protein name**	**Y2H-based PP1 [34]**	**IP + LC–MS/MS [14,37]**	**AP-MS [36]**	**Proximity biotinylation assay [25]**	**Co-IP [7,38–41]**	**TAP-MS [42]**
Ribosomal proteins, large subunit	RPL6		x				
	RPL7		x				
	RPL10		x				
	RPL13	x	x				
Ribosomal proteins, small subunit	RPS2	x		x			
	RPS24		x				
Initiation factors	EIF3G	x					
	EIF4A1						x
	EIF4E				x		
	EIF4E2				x		
	EIF5B						x
Elongation factors	EEF1A1	x	x				x
	EEF1A2						x
Other	FIBRILLARIN		x			x	
	GEMIN5		x			x	

SMN-specific) [2]. This binding influences the initial phases of translation and stabilizes ribosomes in distinct conformations [2], as observed in yeast [59]. These results are in keeping with the hypothesis that SMN may play a role in translation initiation and elongation, as suggested by the interaction with initiation and elongation factors (Table 1). SMN-specific transcripts are characterized by distinct sequence features, including translational enhancer sequences in the 5′ UTR and rare codons within the first five codons of the CDS [2]. These mRNAs are functionally associated with neurogenesis, lipid metabolism, ubiquitination, chromatin regulation, and translation, aligning with processes known to be affected in SMA [2].

In essence, the concept that SMN orchestrates a ribosome-centric platform for regulating mRNA translation offers a distinctive framework for expanding our understanding of the molecular mechanisms underlying the global translational defects observed in multiple models of SMA [2,10,17,19,60].

Direct and indirect translational defects in SMA

Consistent with its essential role in snRNP biogenesis and its interactions with numerous translation-related proteins, a decrease in SMN protein levels below a specific threshold in SMA models is anticipated to hinder translational control of gene expression. Here, we summarize translational deficiencies observed in SMA cellular and mouse models as well as in patients and discuss direct and indirect alterations occurring in various translation-relevant processes, ranging from ribosome biogenesis [61,62] to local translation [63] and beyond [64] (Figure 2).

Global translation

The notion that the SMN protein, aside from its established functions, serves as a regulator of ribosome activity suggests that SMN deficiency may result in localized and early disruptions in translation processes. Global reorganization of cellular, tissue, and patient biofluid proteins can be assessed using proteomics analysis [65]. Global alterations in protein production can also be monitored using metabolic labeling [66] and Surface sensing of Translation (SUnSET) [67], while variations in ribosome recruitment on mRNAs can be analyzed by polysome and ribosome profiling [68,69].

Numerous proteomic investigations have revealed significant changes in global proteomes in animal and cellular models of SMA (for a review, see [65] and [18,52,60,70–72]), such as patient-derived fibroblasts [49,65] and hiPSCs [46]. The majority of these studies were conducted at symptomatic stages of the disease, thus the

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https://doi.org/10.1042/BST20231116

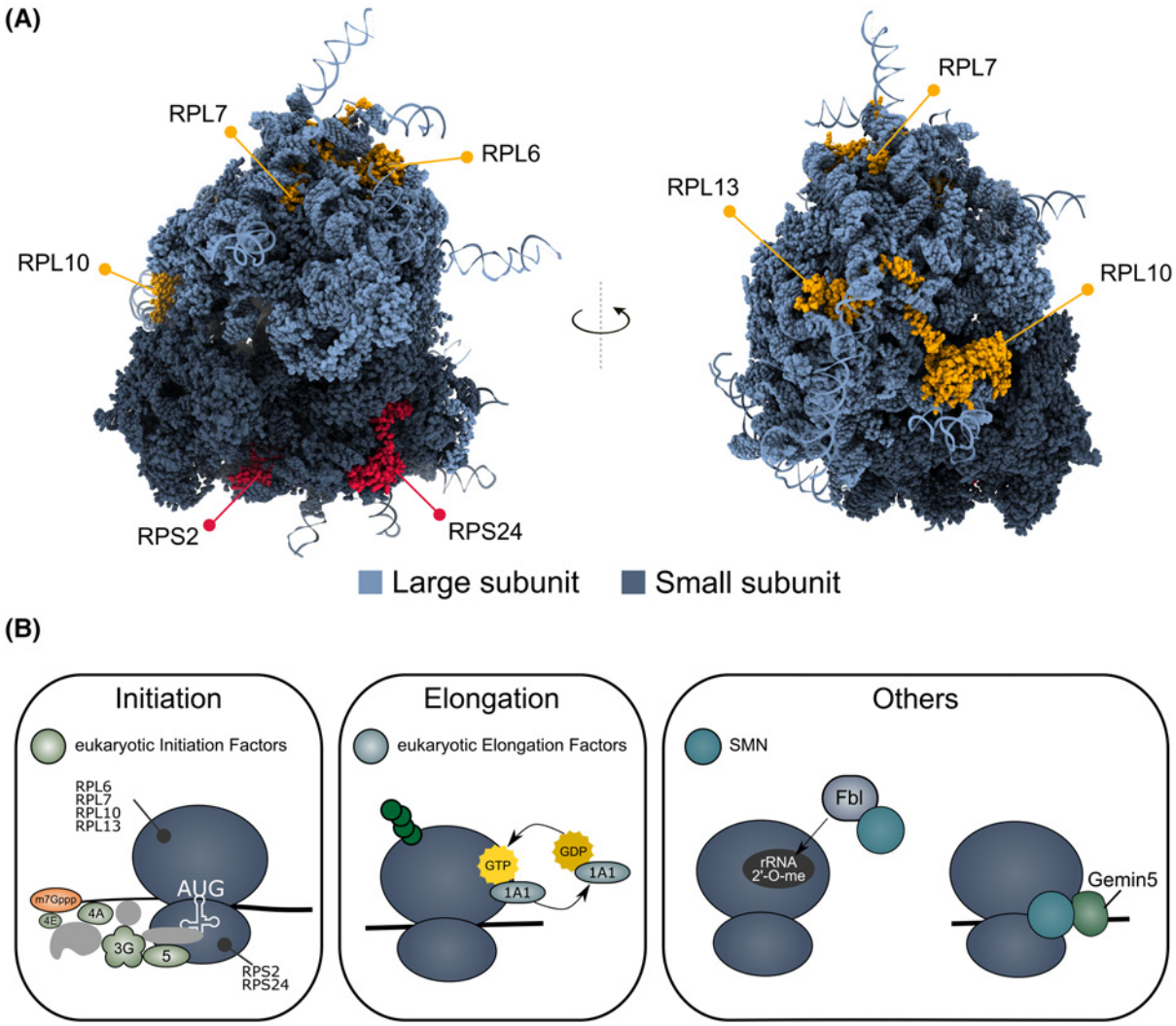

Figure 1. Ribosome-related protein partners of SMN.

(**A**) 4 ribosomal proteins of the large subunit (orange) and 2 ribosomal proteins of the small subunit (red) have been identified as direct interactors of SMN (human ribosome structure from [43]). (**B**) SMN directly interacts with proteins involved in the translation process, including multiple eukaryotic initiation and elongation factors, Fibrillarin and Gemin 5.

cause-effect relationship between SMN deficiency and proteome reorganization is not obvious. However, during embryo development in a mouse model of severe SMA proteomic alterations occur well before the onset of symptoms or the initiation of morphological reorganizations of organs [60].

Proteomic studies in humans and mice revealed reduced levels of ribosomal proteins, elongation, and initiation factors encoded by mRNAs directly bound by SMN [44,45] or enriched in SMN-specific ribosomes [2] (Table 2 and Figure 3). These findings, combined with evidence of reduced ribosome coverage for translation- and SMA-relevant mRNAs, further support the idea that deficiency in SMN levels is linked to translational defects. In primary MNs from SMA mice, SUnSET and Click-iT AHA assays [17,18] show a reduced protein synthesis efficiency, in line with what observed in other primary neurons and cell lines [15–17]. In primary MNs, the level of protein synthesis is strongly affected by SMN loss both in the soma [18] and in the axon [17,18], with a more robust reduction at longer distances from the cell body [18].

Using polysome profiling in early- and latesymptomatic brain, spinal cords, kidney, and brain regions of the mouse model of severe SMA, and in motor neuron-like cell lines with decreased levels of SMN protein, alterations in the percentage of ribosomes in polysomes were observed to be accompanied by loss of SMN

Table 2. RNAs associated with the SMN protein Part 1 of 2

Translation component	Gene name	Interaction: SMN — RNA Hs [44]	Interaction: SMN — RNA Mm [45]	Interaction: SMN-primed ribosomes — RNA Mm [2]	Defects at the translation/protein level
Ribosomal proteins, large subunit	RPL3	x	x	x	x [17,46]
	RPL4	x			x [46,47]
	RPL7		x		x [17,18,48]
	RPL7A	x	x		x [18]
	RPL8	x			x [17,18]
	RPL9		x		x [2,18]
	RPL10A	x			x [18,47]
	RPL12	x			x [17,18,47,49]
	RPL13	x	x		x [18,46]
	RPL13A	x			x [2,17,18,46]
	RPL14			x	x [2,17,18]
	RPL15		x		x [2,17]
	RPL17		x		x [17,46]
	RPL19	x			x [2,18,46]
	RPL21	x		x	x [17,46]
	RPL22L1		x		x [17,18]
	RPL23A		x		x [17,46]
	RPL24		x		
	RPL26	x			x [2]
	RPL17A		x		x [17]
	RPL28	x			x [18,46]
	RPL31		x		x [18]
	RPL35A		x		x [46]
	RPL36	x	x		x [2,17,46]
	RPL36A		x		
	RPL37A	x			x [17]
	RPL41			x	
	RPLP0	x			x [46,47]
	RPLP1			x	x [50,51]
	RPLP2	x			x [18,47]
Ribosomal proteins, small subunit	RPS2	x	x		x [46,48]
	RPS3	x			x [2,17,18,47]
	RPS4X		x		x [17,47]
	RPS5	x			
	RPS6				x [17]
	RPS8	x	x		x [47]
	RPS11				x [18,48]
	RPS12	x	x		x [17,18]
	RPS14		x	x	x [17,18,49]
	RPS15A			x	x [18]
	RPS18	x	x		x [46]
	RPS20				
	RPS21	x	x		x [17]
	RPS23	x	x		x [17]
	RPS25	x	x		
	RPS27A		x		x [17,47]
	RPSA	x	x	x	x [49]
Initiation factors	EIF2B1			x	
	EIF2B5	x			
	EIF2S2	x	x		x [47]
	EIF3A			x	x [46,48,52]
	EIF3M		x		x [2,49]
	EIF4A1	x			x [46]

Continued

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https://doi.org/10.1042/BST20231116

Table 2. RNAs associated with the SMN protein Part 2 of 2

Translation component	Gene name	Interaction: SMN — RNA Hs [44]	Interaction: SMN — RNA Mm [45]	Interaction: SMN-primed ribosomes — RNA Mm [2]	Defects at the translation/protein level
	EIF4A2	x			x [2,17]
	EIF4G1	x		x	x [46]
	EIF5A	x			x [46,53]
Elongation factors	EEF1A1	x		x	x [17,46,53]
	EEF1A2	x			x [52]
	EEF1B2	x			x [47]
	EEF1D	x			
	EEF1G	x			x [46,47]
	EEF2	x		x	x [46,47]
rRNAs	5S		x		
	5.8S	x			
tRNAs	tRNA-Asn		x		
	tRNA-Cys		x		
	tRNA-His		x		
	tRNA-Tyr		x		

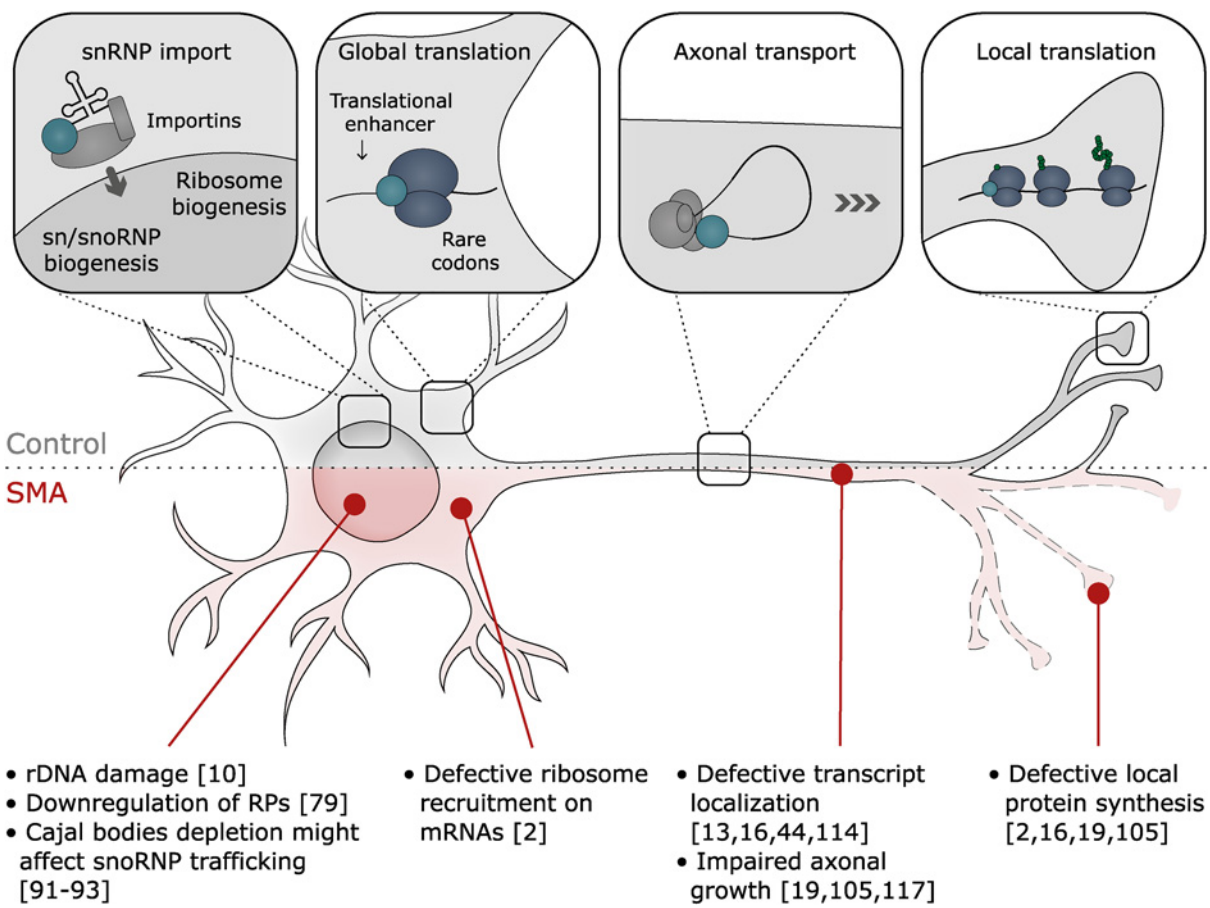

Figure 2. Schematic overview of SMN role in translation and translation-related defects in SMA.

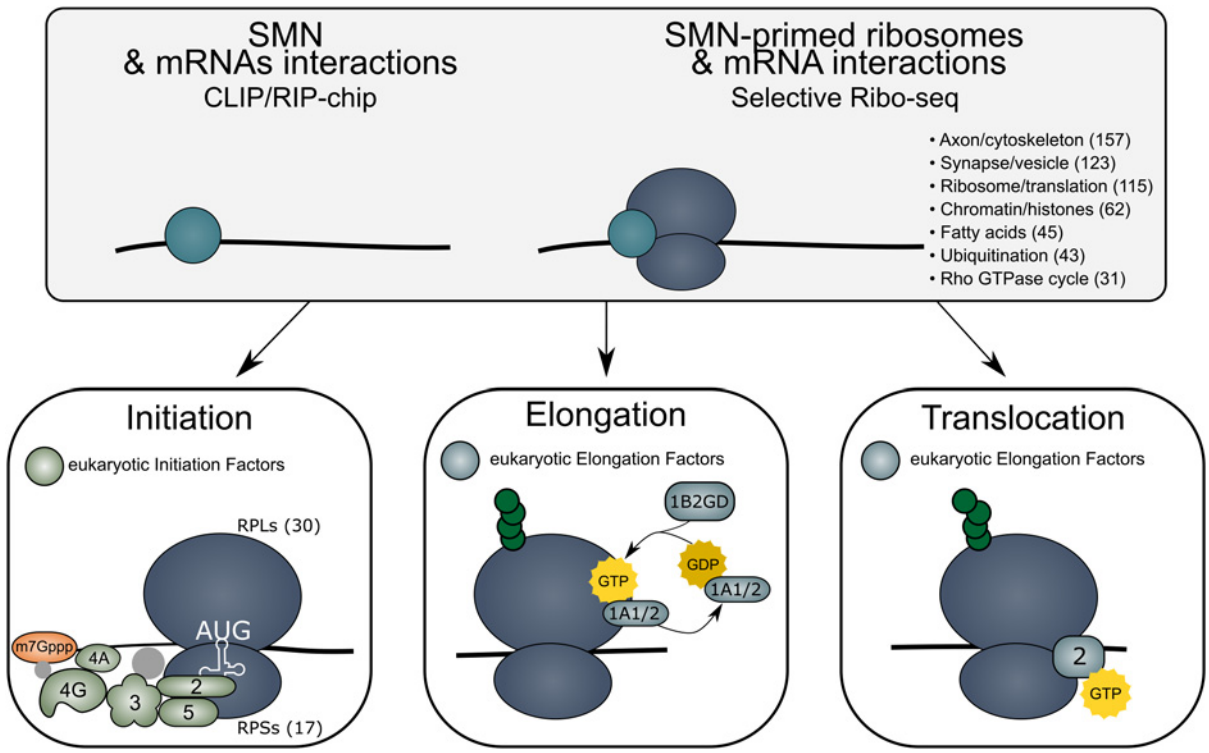

Figure 3. RNAs associated with the SMN protein.

SMN directly interacts with mRNA and functions as a ribosome-associated protein, regulating the translation efficiency of a specific subset of additional mRNAs. This subset, associated with either SMN or SMN-primed ribosomes, encodes proteins crucial to the translation process, including multiple eukaryotic initiation and elongation factors. Numbers in parentheses indicate the number of SMN-specific transcripts associated with each biological process/pathway from [2].

association with ribosomes and polysomes [17]. In addition, a decrease in the number of ribosomes in intercostal nerves of late symptomatic SMA mice [17] and at the ER [45] provides further evidence that SMN loss leads to translation defects that can be rescued by restoring SMN expression using ASO treatment [17]. Interestingly, restoration of SMN levels in patients treated with the small splicing modulator Nusinersen promotes increased protein levels in the cerebrospinal fluid [73].

In light of these observations, it is evident that translation plays a crucial role in SMA, and that it is likely implicated in the pathogenesis of the disease. However, these studies do not clarify whether the changes in protein levels are process/transcript specific or unspecific and directly or indirectly induced by loss of SMN functions in translation. Therefore, this question remains open, especially in patients, where only a limited number of studies observed the direct involvement of SMN loss in translational regulation [13].

In the nucleus: ribosome biogenesis

Fascinating connections between the primary function of SMN protein in snoRNP biogenesis, its role in the nucleus [5–7] and translation deficiencies in SMA can be ascribed to alterations in ribobiogenesis. Given the observed interaction of SMN with proteins involved in pre-rRNA processing such as nucleolin, fibrillarin, protein B23, and GAR1 in human cell lines [7,27,29,30] and healthy human fibroblasts [28], these genes are up-regulated in the spinal cord of a mild model of SMA at the late stage of the disease [74]. Despite no change in the total 45S pre-rRNA levels, a 2-fold increase was observed in the mature 18S rRNA at late stage of the disease [45]. Furthermore, decreased levels in rRNA expression and *de novo* protein synthesis were observed in primary spinal MNs from the SMNΔ7 mouse model [10]. An indirect connection between SMN protein deficiency and alterations in ribobiogenesis was recently proposed as damage of nucleolar rDNA in patient-derived iPSC-MNs [10], potentially impacting the biogenesis of the 40S subunit [75]. However, it remains unclear

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whether the loss of SMN interactions with proteins or noncoding-RNAs involved in ribobiogenesis directly affects rRNA transcription and processing.

A recent single-cell RNA-seq analysis of the spinal cord of a mouse model of SMA revealed the down-regulation of the genes enriched in ribobiogenesis and translation in oligodendrocytes [76]. In line with this finding, the treatment of patient fibroblasts with the small molecule Risdiplam up-regulates genes involved in translation-related processes such as ribosome and ribobiogenesis [77].

Besides being structural components of the ribosome, ribosomal proteins interact with auxiliary factors required for translation and play key roles in rRNA processing, stabilization of secondary rRNA structures, pre-ribosome transport, and RNA folding [78]. Transcripts of ribosomal proteins RPL7, RPL11, RPL24, RPL32, RPL27, RPLP1, RPS4X, RPS20, RPS10, RPS16, RPS25, RPS27a, and RPS29 are down-regulated in the cell body of MNs at the pre-symptomatic stage in the mild mouse model of SMA [79]. These local changes may underlie important defects in neurogenesis, axonal branching, and local translation, as in the case of RPS4X [80]. Moreover, RPS25 is not only required for IRES-mediated translation, but also for ribosome heterogeneity and specialization [81,82], and RPL11, RPS20, RPS25, and RPS27a interact with MDM2 and mediate the p53-dependent ribosomal stress pathway [83–86]. Besides these transcriptional alterations, defects in the recruitment of mRNAs onto polysomes were observed at the early and late stages of the disease in the brain of the severe mouse models of SMA [17]. These changes are accompanied by reduced protein levels of specific ribosomal proteins and diminished ribosome levels in the intercostal nerves during the late stage of the disease [17]. Nevertheless, additional work is needed to understand whether these relatively late changes are responses to preceding alterations before the appearance of symptoms.

In addition to structural components of the ribosome, i.e. rRNA and ribosomal proteins, other essential players in ribobiogenesis are snoRNPs, which are involved in pre-rRNA processing and post-transcriptional modification in nuclear Cajal bodies (CBs). Maturation of snoRNAs and snoRNPs occurs in CBs before their transfer to the nucleolus, where they participate in the pre-rRNA processing [87]. Hence, the depletion of CBs in SMA might affect the trafficking of snoRNAs and snoRNPs between CBs and nucleoli. SMN protein concentrates in CB via interacting with coilin [88–90]. SMN deficiency reduces the number of gems and CBs [91–93] and causes the redistribution of coilin to the nucleolus in MNs from a mild model of SMA and in the post-mortem spinal cord from a 3-month-old patient [94]. Moreover, in SMA-derived fibroblasts, SMN deficiency in CBs was linked to reduced localization of Nopp140 and dyskerin/NAP57, two snoRNP-associated proteins [95], possibly affecting post-transcriptional modifications of rRNA.

Yet, whether SMN plays a direct role in ribobiogenesis through protein–protein or protein–RNA interactions that are lost in SMA is still largely unknown.

Across the nucleus and the cytoplasm: importins and translation

The SMN protein localizes both in the cytoplasm and in the nucleus. In the cytoplasm, it functions as an assembler of the snRNPs spliceosomal complex [96] and it accompanies snRNPs to the nucleus possibly impacting ribosome biogenesis, as discussed previously. In addition, SMN interacts with snurportin1, the importin β receptor [97], and importin β [14]. Whilst snurportin1 plays a role in the nuclear import of the snRNPs complex [98], the class of cytoplasmic importins β is particularly intriguing as they have been recently identified as ribosome-associated proteins [99]. To the best of our knowledge, no studies investigated the potential impact on SMN, importins, and ribosomes cross-talk in SMA. Thus, these new findings introduce an intriguing scenario regarding the potential disruption of this cross-talk in SMA and the impact on the translation and nuclear shuttling of proteins encoded by nuclear-relevant SMN-specific mRNAs [2].

In the cytoplasm: translation-related pathways

SMN protein deficiency may indirectly affect translation through the inactivation of cellular pathways that control protein synthesis in response to various stimuli. The mTOR pathway is a master regulator of protein synthesis and a well-known player in dendrite formation and axonal development during neurogenesis [100–102] with pro-survival effects on spinal MNs [103].

Downstream targets of the mTOR pathway are (i) p70 ribosomal S6 kinase and its target RPS6, the phosphorylation of which activates translation, and (ii) 4E-BP, the phosphorylation of which also promotes cap-dependent translation [64]. Up-regulation of phosphorylated p70 ribosomal S6 kinase occurs in both healthy and SMA fibroblasts upon ATP stimulation; however, this increase cannot rescue changes in the total SMA proteome [24,33]. In control conditions, SMN co-localizes with phosphorylated RPS6 and actin filaments at

sites of *de novo* protein synthesis in membrane protrusions [33] and the phosphorylation of RPS6 is impaired in SMN knockdown primary cortical and spinal MNs [104]. Thelen and co-workers showed that the phosphorylation status of 4E-BP decreases in SMA primary MNs leading to deficient cap-dependent translation, but the use of β-actin as loading control, known to be down-regulated in SMA [105], calls for additional analysis [18]. In fact, the hyperphosphorylation of 4E-BP observed in the brain at the late stage of SMA suggests an up-regulation of protein synthesis [2]. Accordingly, in primary murine MNs with SMN deficiency, the mTOR pathway may be activated during the late stage of neurodegeneration to promote survival and enhance lifespan [104,106]. In line with this result, loganin, a neuroprotective drug, improves the SMA phenotype by increasing the phosphorylation of Akt, which acts upstream of the mTOR pathway, and leads to a modest increase in the lifespan of SMA mice [107]. Muscle tissues from patients also demonstrated an up-regulation of the mTOR pathway [108]. Further investigation is required to elucidate whether RPS6/4E-BP alterations are the consequence or the cause of translational defects in SMA.

mTOR also regulates the actin filaments dynamics and local translation [33,109,110] and SMN interacts with the mTOR transcript [111]. Moreover, SMN deficiency impairs mTOR mRNA transport to the cytoplasm and axon [107] and induces a decrease in actin filaments in the patient's fibroblasts [33]. Despite these observations, the role of mislocalization or down-regulation of mTOR and mTOR-related transcripts on its downstream targets and translation is a matter of further investigation.

Interestingly, the knockdown of the negative regulator of the mTOR pathway *Pten* triggers axonal growth via increasing the levels of RPS6 in SMN-deficient primary MNs [106], suggesting that positive regulation of translation may be beneficial to SMA. Consistently, a mild mouse model of SMA treated with siRNA against *Pten* resulted in 35% increase in the number of MNs [106].

ER stress activates the integrated stress response (ISR) via the PERK pathway, which results in the phosphorylation of the eIF2α, inhibition of translation initiation, and overexpression of apoptotic or heat shock genes [112,113]. Activation of the ISR was observed in a *Caenorhabditis elegans* SMA model [113], in hiPSC-derived MNs from patients, and in the spinal cord of a mild mouse model of the disease [82]. Pharmacological inhibition of the ER stress exerts mild improvement in mice lifespan [80]. Notably, in a severe SMA mouse model, significant translation defects were noted at the early stage of the disease and were attributed to the loss of SMN-ribosome interactions. Since no alterations in p-eIF2α were observed, either at early or late stages of SMA [2], the translation defects induced by pathway activation are likely late features during disease pathogenesis.

mRNA transport and local translation

According to the role of SMN in the assembly of mRNP granules, mRNA binding [44], and transport, defects in the localization of several transcripts in the axon have been observed in SMN-deficient cells [13,16,44,114]. Reduced axonal localization of *Actb* [105], *Gap43* [16,115], and *RPS6* [24] impact axonal growth through deficient local translation [19]. Deficiency of SMN causes the altered assembly of axonal mRNP granules [44,116,117] also due to loss of SMN/α-COP interaction [118]. The involvement of SMN in the formation and control of RNA granules, which play crucial roles in axonal transport, is closely connected to local translation [2,16,19,105,117,119]. Defective local translation [19] and disruption of cytoskeleton and ubiquitin homeostasis [22] are likely to induce the devastating alterations observed at the neuromuscular junction (NMJ), an early pathogenic marker of SMA [120,121]. Here, numerous defects in mRNA transport, translation, and proteostasis of pivotal proteins for NMJ maturation and functional maintenance have been reported [2,22,79,122].

These alterations may be connected to decreased interaction between SMN and RBPs involved in the regulation of mRNA transport along axons [123] and local translation [63]. SMN not only associates with RBPs that are known ribosome-associated proteins and translation factors, such as FMRP [119,124], and with translational enhancers such as HuD [16,125], but it also localizes at the plasma membrane [33], modulating the synthesis of the ribosomal protein RPS6 [24]. Notably, following stimulation of primary and SMN-deficient MNs using brain-derived neurotrophic factors, the ribosomal subunits fail to form fully assembled ribosomes at the axon terminal, leading to impaired localized translation and ER remodeling [19]. These findings support the idea proposed by Lauria et al. [2] that SMN serves as a ribosome-associated protein, facilitating active translation. As such, SMN plays a crucial role in preserving vital housekeeping functions necessary for ribosome assembly, regulating local translation, and coordinating interactions between the translational machinery and other organelles.

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https://doi.org/10.1042/BST20231116

Opportunities for translation-based therapies

Three approved therapies for SMA, including Zolgensma, Spinraza, and Evrysdi, aim to enhance full-length SMN protein levels [20,126]. Whilst these treatments improve patients' survival, quality of life, and motor functions [127–129], they do not offer a definitive cure. Heterogeneity in symptoms, age of onset, and treatment response highlight significant unmet needs that persist among patients, emphasizing the necessity for further research and development of complementary therapies. The forefront of clinical research is exploring combinatorial strategies alongside existing treatments [126]. 'SMN-independent' approaches are used in addition and combination with existing and new SMN-dependent therapies [126,130,131], to address affected pathways, and potentially provide additive or synergistic benefits for patients [126].

One appealing and largely unexplored addition to existing SMN-independent therapies lies in correcting translational defects and leveraging translation as a still relatively unexplored pathway affected in SMA. Improving SMN-specific protein synthesis or increasing the availability of translationally down-regulated targets may prove advantageous.

The large majority of available therapies targeting mRNA translation are cancer drugs aiming at reducing protein synthesis rates. However, in SMA translation is generally down-regulated, and more broadly, the dysregulation of protein homeostasis and folding is a common feature of a wide range of neurodegenerative disorders [132]. In these cases, the up-regulation of translation could be beneficial [133]. Among the few compounds boosting translation, ISRIB blocks the PERK branch of the unfolded protein response leading to a partial restoration of translation in prion diseases [132] and amyotrophic lateral sclerosis (ALS) [134]. As aforementioned, the activation of ISR has been observed in some models of SMA at the late symptomatic stage [113,135], but there is no evidence of eIF2α phosphorylation at early and late symptomatic stages in a different model [2]. Therefore, as of now, there is no clear evidence demonstrating the widespread activation of the ISR in multiple SMA models. Moreover, ISR activation at the late symptomatic stage in the mild model of SMA suggests this might be a consequence rather than a driver of the disease. Thus, it is yet to be established whether small molecules such as fosigotifator might be beneficial in SMA, and innovative avenues to increase the protein synthesis level should be explored.

Among these, repurposing of orphan drugs remains a crucial goal as it would help reduce the cost and time of clinical trials [136–138]. To identify candidate drugs for translational enhancement, platforms for novel drug screening must be developed to use as a readout of the translational activity of transcripts bearing SMN-specific features, such as translational enhancers and rare codons [2]. As an alternative strategy, the up-regulation of translationally down-regulated targets may also be beneficial. Therefore, it remains crucial to strengthen research on SMN translational targets and its partners. We foresee that this, along with the rapid evolution of RNA therapies, will represent a major stepping stone in the development of complementary therapies for SMA and other related diseases.

Perspectives

- SMN interacts with ribosomes, as well as mRNAs and proteins associated with translation, creating a translation platform that relies on SMN.
- Deficiencies in SMN lead to widespread translational defects in various disease models, affecting protein homeostasis.
- Enhancing the levels of SMN-specific proteins or mRNAs could offer new opportunities for SMN-independent therapeutic interventions.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Funding

G.V. is grateful for funding from the European Union's Horizon 2020 Research and Innovation Program under the Marie Skłodowska-Curie grant (H2020 Marie Skłodowska-Curie Actions) agreement no. 956185 (SMABEYOND

ITN), AFM Telethon (#23692); Telethon (GGP19115 and GMR23T1048); EU funding within the MUR PNRR 'National Center for Gene Therapy and Drugs based on RNA Technology' (Project no. CN00000041 CN3 RNA); Fondazione Caritro.

Author Contribution

G.S., M.P., F.L., E.P., and G.V. performed the literature search and wrote the manuscript. M.P., F.L., and E.P. designed the figures. G.V. conceived the manuscript, supervised the work, and obtained the funding. All authors approved the manuscript.

Acknowledgments

The authors wish to thank all members of the Laboratory of Translational Architectomics (IBF-CNR Italy) for valuable suggestions and comments.

Abbreviations

ISR, integrated stress response; MN, motor neuron; SMA, spinal muscular atrophy; SMN, survival motor neuron.

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