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Review

The SMN complex

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Abstract

The survival of motor neurons (SMN) protein is the product of the disease-determining gene of the neurodegenerative disorder spinal muscular atrophy (SMA). SMN is part of a stable multiprotein complex that is found in all metazoan cells in the cytoplasm and in nuclear Gems. The SMN complex contains, in addition to SMN, at least six other proteins, named Gemins2–7, and plays an essential role in the assembly of the spliceosomal small nuclear ribonucleoproteins (snRNPs). Through its binding to specific sequences in the snRNAs, the SMN complex surveys the correct identity of the target RNAs and facilitates snRNP assembly. Based on its ability to interact with several other protein and RNA components of cellular RNPs, it is likely that the SMN complex functions as an assemblyosome in the formation of diverse RNP particles, some of which may be of particular importance to the motor neuron. A detailed understanding of the cellular roles of the SMN complex may help the development of therapeutic strategies for this neurodegenerative disease.

Keywords: SMN; Neurodegenerative disorder; Atrophy

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that is characterized by the degeneration of α motor neurons in the anterior horn of the spinal cord. This loss of lower motor neurons leads clinically to progressive muscular weakness, dysphagia, dyspnea, and in the severe cases, to death [1]. SMA affects approximately 1 in 6000 live births and is the leading genetic cause of infant mortality [2]. Genetic analysis and physical mapping in SMA patients led to the identification of a gene named "survival of motor neurons" (*SMN*) as the disease gene for SMA [3]. In humans, the *SMN* gene is duplicated as an inverted repeat in a 500-kilobase region of chromosome 5 at locus 5q13 [3]. Over 98% of SMA patients harbor deletions or loss-of-function mutations in the telomeric copy of the *SMN* gene (*SMN1*) but retain at least one copy of the centromeric form (*SMN2*) [3]. The centromeric gene is nearly identical to its telomeric neighbor; however, a single point mutation in exon 7, the last coding exon, modifies its splicing pattern toward skipping of this exon [4]. As a consequence, *SMN2* produces predominantly an exon 7-deleted and functionally defective form of the SMN protein that lacks 16 amino acids at the carboxyl terminus. This truncated protein appears to be unstable and cannot substitute for full-length SMN, which is the primary protein product of the *SMN1* gene. Hence, the *SMN2* gene with its altered splicing profile fails to protect from the disease, which is caused by reduced levels but not the complete absence of the SMN protein [4]. In general, the severity of SMA correlates well with the amount of SMN protein in patient cells [5].

The SMN protein is ubiquitously expressed in all tissues of metazoan organisms reflecting the fact that it provides a fundamental activity required by all cells. Moreover, SMN is essential in divergent organisms including human, mouse, chicken, *Caenorhabditis elegans*, and *Schizosaccharomyces pombe* (reviewed in Ref. [6]). Why low levels of SMN protein in the cells of SMA patients lead to the specific loss of motor neurons remains a central question in this field.

SMN is found in the cytoplasm and enriched in nuclear Gems

In humans, SMN is a protein of 294 amino acids that is found in the cytoplasm and the nucleus of cells, where it is

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present throughout the nucleoplasm and is highly enriched within discrete bodies called Gems (for "Gemini of Cajal bodies"; Fig. 1; [7]). As suggested by their name, Gems are similar in size and number to Cajal bodies and are often associated with them [7]. Cajal bodies were first described in 1903 and are known to contain high levels of factors involved in the transcription and processing of many types of nuclear RNAs, including small nuclear ribonucleoproteins (snRNPs), nucleolar ribonucleoproteins (snoRNPs), and the three eukaryotic RNA polymerases [8,9]. However, since Cajal bodies are deficient in DNA, nascent pre-mRNA, and non-snRNP essential splicing factors, they are probably not active sites for transcription or splicing [8]. Instead, they most likely are locals where the assembly and/or modification of the nuclear transcription and RNA processing machineries takes place [9]. Double-label immunofluorescence microscopy using antibodies against SMN as a marker of Gems, and p80-coilin as a marker of Cajal bodies [10], revealed that Gems and Cajal bodies mostly colocalize in some cell lines and adult tissues but are separate in fetal tissues and several types of cultured cells (Fig. 1; reviewed in Ref. [6]). This indicates that Gems and Cajal bodies are distinct nuclear structures that have a dynamic functional relationship. The interaction between Gems and Cajal bodies may be mediated, at least in part, by the capacity of SMN and coilin to bind each other [11]. Gems are also separate from interchromatin granule clusters (or speckles), which are DNA-free nuclear domains composed of densely packed ribonucleoprotein particles enriched in mature snRNPs and protein splicing factors [12]. Interestingly, depletion of SMN via RNA interference in living HeLa PV cells leads to the complete disappearance of Gems (W. Feng and G. Dreyfuss, unpublished data). This demonstrates that SMN serves as an essential building block

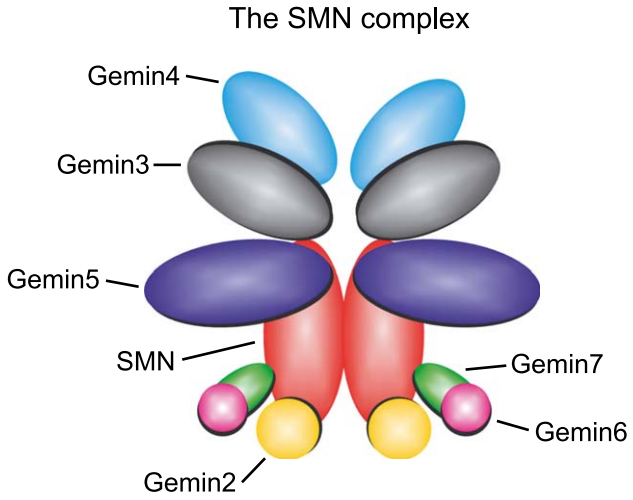

Fig. 2. The SMN complex. Schematic representation of the SMN complex. Gemins2, 3, 5, and 7 bind directly to SMN, while Gemins4 and 6 are associated through direct interaction with Gemins3 and 7, respectively. For simplicity, the SMN complex is illustrated in dimeric form although, from its size (30–70S), it most likely is a much larger oligomeric structure.

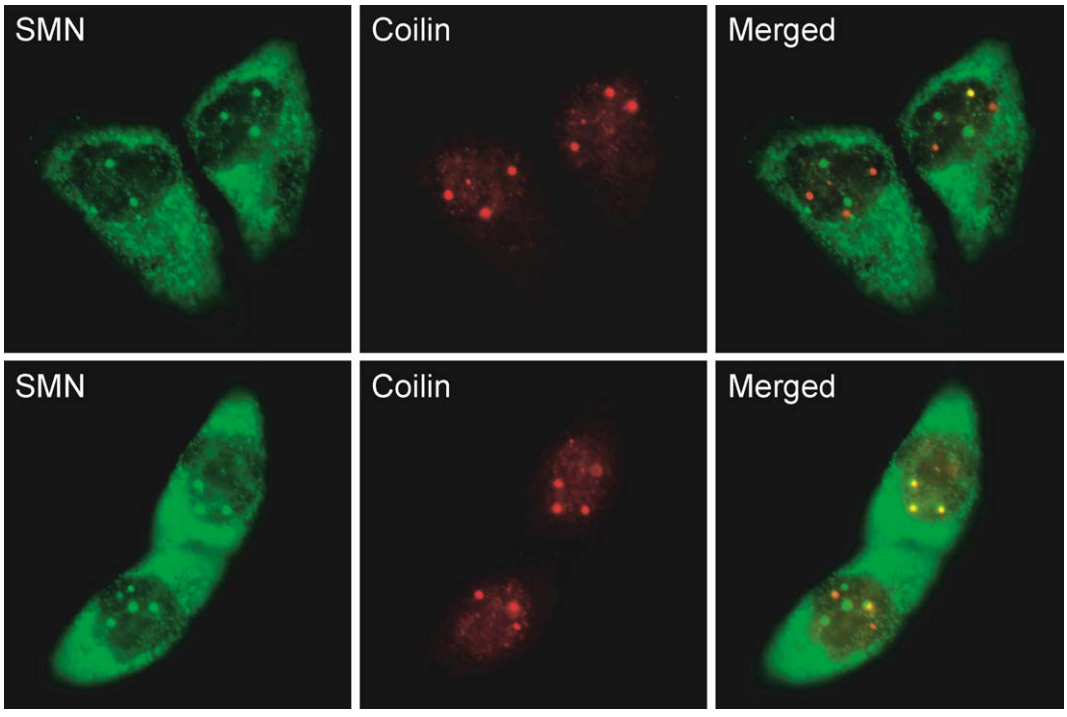

Fig. 1. SMN is found in the cytoplasm and enriched in nuclear Gems. Double-label immunofluorescence microscopy using anti-SMN (2B1; 1:500; left panels) and anti-p80-coilin antibodies (R288, 1:1000; middle panels) on HeLa PV cells. Colocalization results in a yellow signal (superimposed images are shown in panels on the right). Note that Gems and Cajal bodies are often entirely separated.

of these nuclear bodies. However, although Gems contain high levels of SMN and also several SMN-interacting proteins, their specific function, if any, is currently not known.

SMN functions as part of a multiprotein complex

The SMN protein oligomerizes and forms a stable complex called the SMN complex, with a group of proteins named the Gemins. These include Gemin2 (formerly SIP1), Gemin3/DP103 (a DEAD-box RNA helicase), Gemin4, Gemin5/p175 (a WD repeat protein), Gemin6, and Gemin7 (Fig. 2; Table 1; [13–20]). This complex is large and sediments in sucrose gradients as hetero-disperse particles of 30–70S [6]. The Gemins colocalize with SMN in Gems and are also present throughout the cytoplasm and, albeit at lower levels, in the nucleoplasm [13,14,16,18–20]. Gemin4 is the only SMN complex component that also localizes to the nucleolus [16]. Based on their stable association with SMN, the Gemins can be considered as integral components of the SMN complex and are readily isolated by co-immunoprecipitation using anti-SMN antibodies or antibodies to the Gemins, even under stringent high salt conditions (750 mM NaCl; [6]). Gemins2, 3, 5, and 7 interact directly with SMN, while Gemin4 and Gemin6 may be indirectly associated as they require binding to Gemin3 and Gemin7, respectively, for association with the SMN complex [13,14,16,18–20]. The most prominent structural motifs within the amino acid sequences of the Gemins are a DEAD-box motif in Gemin3 [14,15] and an array of 13 WD repeats in Gemin5 [18]. As RNA helicases have been implicated in nearly all processes related to RNA metabolism [21], it is likely that the helicase activity [22] and predicted ATPase activity of Gemin3 are critical for the SMN complex, in its entirety, to function in the assembly of ribonucleoproteins (see below). However, direct evidence thereof is still lacking. The presence of multiple WD repeats in Gemin5 implies that this protein may engage in multiple protein interactions and perhaps serve as a platform for the assembly of protein complexes.

Table 1
SMN complex components

Protein	Molecular weight (kDa)[a]	Localization	Comments	References
SMN	37	cyt., nucl., Gems		[3]
Gemin2	31.5	cyt., nucl., Gems		[13]
Gemin3	103	cyt., nucl., Gems	DEAD-box RNA helicase, component of microRNPs	[14,15]
Gemin4	97	cyt., nucl., Gems, nucleolus	component of microRNPs	[16]
Gemin5	168.5	cyt., nucl., Gems	WD repeats, coiled coil	[17,18]
Gemin6	15	cyt., nucl., Gems		[19]
Gemin7	14.5	cyt., nucl., Gems	two RG pairs and one GRR	[20]

Abbreviations: cyt., cytoplasm; nucl., nucleoplasm.
[a] As apparent by SDS-PAGE electrophoresis.

Interaction of the SMN complex with other proteins

The SMN complex interacts with several proteins, some of which can be considered SMN complex substrates. Among these substrates are the Sm proteins and Sm-like (Lsm) proteins of the snRNPs, which are essential components of the splicing machinery. Intriguingly, each component of the SMN complex has the capacity to bind to a subset of the Sm/Lsm proteins [13,14,16,18–20]. Additional SMN complex substrates are the snoRNP proteins fibrillarin and GAR1, as well as hnRNP U, Q and R, RNA helicase A, coilin, nucleolin, and Epstein–Barr virus nuclear antigen 2 [11,23–28]. Most of the SMN complex substrates identified thus far are constituents of various RNP complexes and contain sequence domains enriched in arginine and glycine residues. These RG-rich domains were shown to mediate the binding to the SMN complex [23,28–31], and this motif amongst these binding partners may explain how the SMN complex can recognize such a multitude of different substrates. Moreover, modification of specific arginine residues within these RG-rich domains by symmetrical dimethylation greatly enhances the affinity of several of these substrates to SMN [28,29,31]. This post-translational modification is carried out by a 20S arginine methyltransferase complex, the methylosome, that contains the methyltransferase JBP1/PRMT5, pICln, and MEP50 (a WD repeat protein) [32–34].

Recently, it was also reported that protein phosphatase 4 (PPP4), a ubiquitous essential protein serine/threonine phosphatase, is associated with the SMN complex via binding to Gemin4 and/or Gemin3, and overexpression of catalytic (PPP4c) and regulatory (R2) domains of PPP4 was found to modify the temporal localization of newly formed snRNPs in HeLa cells [35]. However, whether and how this protein phosphatase affects the functions of Gemin3, Gemin4 and/or the SMN complex awaits further clarification. Gemins3 and 4 have also been shown to be components of a 15S microRNP complex that contains eIF2C2, a member of the Argonaute protein family, and numerous miRNAs [36,37]. These findings raised the interesting possibility that SMN deletions or loss-of-function mutations in SMA patients may also affect the activity of miRNPs by, for example, affecting the balance of the shared complex components Gemins3 and 4 between SMN complexes and miRNPs [37]. Finally, the list of proteins reported to interact with SMN also includes several proteins that neither contain RG-rich motifs nor interact with RNPs, such as profilin, the FUSE binding protein, ZRP1, p53, and the NS1 protein of minute virus of mice ([38]; reviewed in Ref. [6]). The functional significance of these interactions is presently difficult to assess.

The SMN complex plays an essential role in the assembly of snRNPs and possibly other RNPs

It is of note that most SMN complex substrates characterized so far are components of various RNP complexes that are involved in diverse aspects of RNA processing. It therefore became apparent that the SMN complex might take part in many aspects of cellular RNA metabolism. Indeed, a well-characterized function of the SMN complex is its role in the assembly of the spliceosomal snRNPs (reviewed in Ref. [39]). Using cell extracts and affinity-purified components, it was shown that the SMN complex is essential and sufficient to mediate the ATP-dependent assembly of the seven-membered ring of the common Sm proteins around a highly conserved sequence motif of less than 10 nucleotides, called the Sm site, present in most snRNAs. Moreover, the SMN complex was found to function as a specificity factor for this assembly process by ensuring that Sm cores are only formed on the correct RNA molecules [40]. The ability of the SMN complex to facilitate and safeguard accurate snRNP assembly is based on its capacity to bind both Sm proteins and also snRNAs. Indeed, the SMN complex binds directly with high affinity and in sequence-specific manner to several snRNAs [41,42]. These observations suggest that the SMN complex brings the protein and RNA components together for snRNP assembly, thus serving as a genuine assemblyosome for Sm cores on snRNAs. Clearly, in the intricate microenvironment of the cell, a stringent specificity of snRNP assembly is of pivotal importance since haphazard binding of Sm proteins to nontarget RNAs would interfere with the functions of these RNAs. Thus, the SMN complex is not only an essential mediator of snRNP assembly but also provides stringent control over this process.

Aside from its roles in snRNP assembly, the SMN complex most likely functions in the formation of other RNPs. For example, based on its direct interactions with fibrillarin and GAR1, two protein constituents of box C/D and box H/ACA snoRNPs, respectively, the SMN complex may play a role in the biogenesis of snoRNPs, which are involved in the posttranscriptional processing and modification of ribosomal RNAs [23,24]. Furthermore, a dominant negative mutant of SMN, SMNΔN27, inhibits pre-mRNA splicing in vitro [43]. Transient expression of this mutant in HeLa cells leads to a dramatic reorganization of snRNPs and the RNA polymerase II (Pol II) transcription and processing machinery in the nucleus, probably by impairing the regeneration of functionally active snRNPs or other components of the spliceosome and the components of the Pol II transcription complex [30,43]. The involvement of the SMN complex in the biogenesis of the Pol II transcription factories may be mediated by its ability to interact with RNA helicase A, which binds Pol II and functions in transcription [30,44].

Recent reports have also suggested specific roles for SMN in the motor neuron. Studies in zebrafish using SMN-specific antisense morpholinos to knock down the SMN protein level throughout the entire embryo revealed motor axon-specific pathfinding defects [45]. Furthermore, primary motor neurons isolated from a transgenic SMA mouse model were reported to exhibit reduced axon growth in culture when compared to motor neurons isolated from wild-type mice [46]. The same study also showed that overexpression of SMN and hnRNP R in differentiating PC12 cells promotes neurite outgrowth and modulates the localization of β-actin mRNA in neurites, thus raising the possibility that SMN is involved in the transport of specific mRNA molecules in motor axons [46]. However, whether the clinical symptoms of SMA are caused by deficiencies in functions of SMN that are specific to the motor neuron or common to all cells but at higher demand in this cell type must still be resolved.

Conclusion

There is now ample evidence that SMN, in the context of the multiprotein SMN complex, is intimately involved in the assembly of spliceosomal snRNPs and possibly other RNP particles. Detailed molecular studies of snRNP assembly revealed that SMN is not only essential for the assembly of Sm cores on the snRNAs but that it also serves as a critical specificity factor in this process. Considering the ability of SMN to bind protein and RNA components of other RNPs, its role as an assemblyosome may be more general and include the biogenesis of other RNP formations, possibly some that are specific to, or of special importance in, the motor neuron. Future investigation of the biochemical defects in the cells of SMA patients will hopefully elucidate the precise molecular deficiencies that lead to the degeneration of motor neurons.

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