Small nuclear RNAs and mRNAs: linking RNA processing and transport to spinal muscular atrophy

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Abstract

The splicing of pre-mRNA by the spliceosome is a characteristic feature of eukaryotic cells, dependent on a group of snRNPs (small nuclear ribonucleoproteins). These splicing snRNPs have a complex assembly pathway involving multiple steps that take place in different regions of the cell, which is reflected in their complex subcellular distribution. Vital to the assembly of splicing snRNPs is the protein SMN (survival of motor neurons). In multicellular organisms, SMN acts in the cytoplasm, together with its associated protein complex to assemble a heptameric ring of proteins called the Sm proteins as an early stage in splicing snRNP assembly. A deficiency of the SMN protein results in the inherited neurodegenerative condition SMA (spinal muscular atrophy), a leading cause of infant mortality specifically affecting spinal motor neurons. It has long been a puzzle how lowered levels of a protein required for a process as fundamental as splicing snRNP assembly can result in a condition with such a definite cell-type-specificity. The present review highlights recent research that points to wider roles in RNA metabolism for both SMN itself and the Sm proteins with which it is linked.

Splicing snRNP (small nuclear ribonucleoprotein) biogenesis and the role of survival motor neurons

In eukaryotic cells, a vital regulatory mechanism during gene expression is splicing of the pre-mRNA (precursor mRNA), transcribed directly from the DNA sequence, into a mature mRNA ready for export to the cytoplasm and subsequent translation to form functional proteins. During splicing, intron sequences are removed and protein-coding sequences are retained. Splicing is often complex, involving multiple splice-site choices, and is carried out by a macromolecular machine termed the spliceosome.

The splicing snRNPs (U1, U2, U4-U6 and U5) are a group of snRNPs with essential roles at the core of the spliceosome. With the exception of U6 snRNP, the splicing snRNPs comprise a core small nuclear RNA (snRNA: U1 snRNA etc.) and a heteroheptameric ring of proteins termed the Sm proteins (SmB/B', SmD1, SmD2, SmD3, SmE, SmF and SmG). This ring of Sm proteins binds around the U-rich Sm site in the snRNA [1]. Each of the splicing snRNPs also contains several snRNP-specific proteins not found in the other snRNPs, for example U1 snRNP contains U1A, U1C and U170K. U6 snRNP is unusual among the spliceosomal snRNPs as it contains a core ring of LSm (like Sm) proteins, which are related to, but distinct from, the Sm proteins contained in the other splicing snRNPs [2]. Transcription of the snRNA cores of the Sm snRNPs (U1, U2, U4 and U5) by RNA polymerase II occurs in the nucleus [3] and the mature snRNPs carry out their functions in pre-mRNA splicing in the nucleus. Despite this, in the cells of mammals and other multicellular organisms studied to date, the Sm snRNPs undergo processing and early assembly stages in the cytoplasm, with the snRNAs being exported from the nucleus immediately after transcription (Figure 1). A key cytoplasmic event is the assembly of the Sm protein heptameric ring around the snRNA. This requires two distinct protein complexes: the PRMT5 (protein arginine methyltransferase 5) complex, responsible for methylating the N-terminal tails of SmB, SmD1 and SmD2; and the SMN (survival of motor neurons) complex, responsible for assembling the Sm protein ring on to the Sm site of the snRNA (reviewed in [4]). SMN and its associated proteins are hypothesized to serve roles as chaperones, preventing the assembly of Sm protein rings on inappropriate RNA targets. This is also proposed as a partial explanation for the convoluted subcellular pathway of splicing snRNP maturation [5]. The presence of the Sm protein ring on the newly assembled snRNP is a requirement for its re-import into the nucleus. Although the major complexes involved in Sm protein addition to the snRNAs are known, the precise physical organization of these events within the cytoplasm is not clear.

In addition to being present in the cytoplasm, SMN also accumulates in discrete bodies within the nucleus called gems

Key words: messenger ribonucleoprotein (mRNP), Sm protein, small nuclear ribonucleoprotein (snRNP), spinal muscular atrophy.

Abbreviations used: CB, Cajal body; LSm, like Sm; miRNA, microRNA; mRNP, messenger ribonucleoprotein; pre-mRNA, precursor mRNA; PRMT5, protein arginine methyltransferase 5; SMA, spinal muscular atrophy; SMN, survival of motor neurons; snRNP, small nuclear ribonucleoprotein.

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Figure 1 | Simplified diagram of splicing snRNP assembly

The newly transcribed snRNA is exported to the cytoplasm (grey and black circles represent proteins of the snRNA export complex), where the PRMT5 and SMN complexes are required for assembly of the Sm protein core. Partially mature snRNPs are then imported back into the nucleus (grey circles represent proteins of the snRNP import complex), where they interact transiently with the CB/gem before accumulating in speckles.

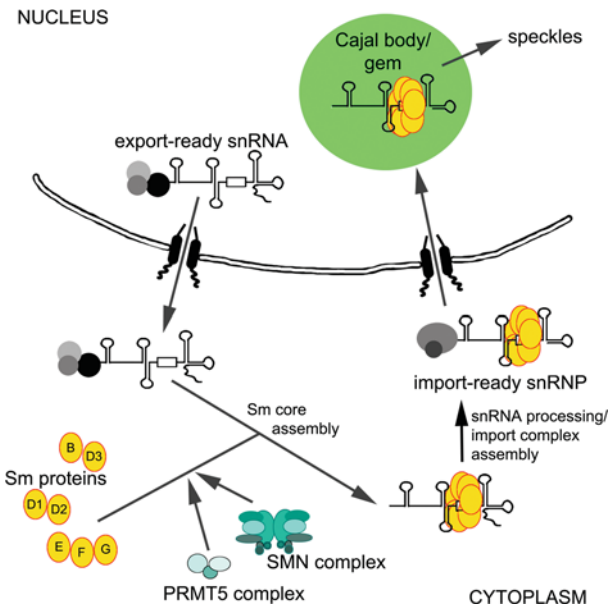
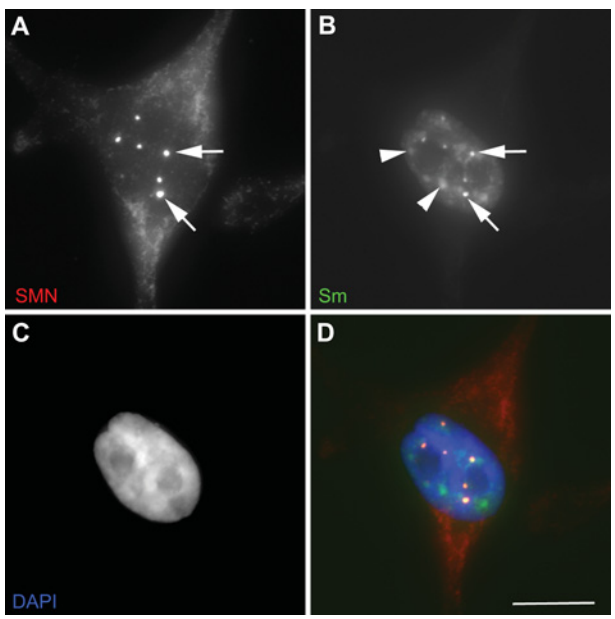


Figure 2 | Overlapping localizations of SMN and splicing snRNPs in HeLa cells

The SMN protein (**A**, and red on overlay, **D**) localizes predominantly in the cytoplasm with nuclear signal restricted to CBs/gems (arrows). Splicing snRNPs (**B**, and green on overlay, **D**) detected using anti-Sm antibodies are largely, but not completely, restricted to the nucleus showing accumulation in CBs/gems (arrows) and speckles (arrowheads). The nucleus is stained with DAPI (4′,6-diamidino-2-phenylindole) (**C**, and blue on overlay, **D**). Scale bar represents 10 μm.



[gemini of CBs (Cajal bodies)] [6] (Figure 2). Its precise role in this location is unclear, but the closely related, and frequently spatially coincident, nuclear CBs play a key role in the maturation and recycling of splicing snRNPs, which accumulate in CBs. The subcellular localization of splicing snRNPs is also complex. The predominant localization of snRNPs is in nuclear speckles or interchromatin granule clusters (reviewed in [7]), multiple irregularly shaped structures in which many different splicing factors, including snRNPs, are thought to be stored allowing them to be recruited rapidly to sites of active pre-mRNA splicing as required. In many cell types, splicing snRNPs are also found in nuclear CBs and, occasionally, nucleoli. Experiments using pulsed expression of fluorescent-protein-tagged Sm proteins to specifically label newly assembled snRNPs in the cytoplasm have implicated CBs as the site of further maturation of newly assembled snRNPs following their re-import from the cytoplasm. The identification of specific scaRNAs (small CB RNAs) [8,9], localized in CBs and capable of modifying U snRNAs, further connect this transient physical localization with molecular events in the splicing snRNP maturation pathway.

In addition to the major spliceosome, eukaryotic cells also contain the more recently discovered and less well characterized minor spliceosome. The minor spliceosome is responsible for the splicing of a divergent class of intron, representing approximately 0.34 % of introns in the human genome [10], and contains a different repertoire of snRNPs from that of the major spliceosome. The minor spliceosomal U11–U12 dimer replaces U1 and U2 snRNPs, whereas an alternative U4–U6 dimer replaces its equivalent from the major spliceosome. Although the details of minor spliceosomal snRNP assembly have not been widely studied, the assumption is that they follow an equivalent biogenesis pathway to those of the major spliceosome (reviewed in [11]).

SMA (spinal muscular atrophy): a motor neuron-specific condition linked to snRNP maturation

The SMN complex has received particular attention because the SMN protein, for which it is named, is known to be present at insufficient levels in patients with the inherited neurodegenerative condition SMA [12,13]. SMA is an autosomal recessive neurological disease in which motor neurons of the spinal cord degenerate leading to loss of movement and, in its most severe form, death from respiratory failure within the first 2 years of life. SMA is the most common genetic cause of infant mortality, affecting one in every 6000 births. There is currently no cure and little in the way of treatment for SMA patients. Although the genetic defect responsible for SMA has been known for some time,

together with at least one confirmed role for the protein [14,15], there are still many questions unresolved about the molecular pathology of the condition. A particular puzzle is the cell-type-specificity of the damage seen, with spinal motor neurons apparently exquisitely sensitive to decreased levels of the SMN protein. Several recent studies have suggested that there may also be defects in other cell types such as muscle and sensory neurons (reviewed in [16]), but the vast majority of cell types appear to be unaffected despite the well-known housekeeping role of SMN in splicing snRNP assembly. It has been proposed that motor neurons simply require a higher rate of splicing snRNP production than any other cells. This, however, seems implausible: although motor neurons are huge cells with highly specialized functions, they are post-mitotic. *In vitro* studies suggest that snRNP maturation is at its maximum in rapidly dividing cells [17,18], so a direct correlation between demand for snRNP maturation and sensitivity to lowered SMN levels might be expected to produce symptoms in rapidly renewing cells.

Does splicing snRNP deficiency lead to splicing defects in genes essential for motor neurons?

Although a simplistic explanation of motor neurons having particularly high demand for splicing snRNP assembly seems unlikely, previous studies have identified altered profiles of splicing snRNPs in cell culture and mouse models of SMA [19,20]. These changes appear predominantly to affect the less abundant snRNPs of the divergent minor spliceosome and, of particular relevance to the pathology of SMA, are different in different cell types. The reason for a more marked effect of depleted SMN on levels of the minor snRNPs is unclear. In parallel with the altered snRNP profiles, widespread defects in splicing have been found in numerous models of SMA [19–23], affecting introns spliced by both spliceosomes, whereas alterations in the dynamics of splicing snRNPs within the nucleus, proposed as a mechanistic link between snRNP depletion and aberrant splicing, also affect both the minor and major snRNPs [24]. Whatever the basis for the altered splicing seen in SMA models, the selective effect on minor spliceosomal snRNPs has led to a search for genes containing minor introns that may be particularly important in motor neurons. Recent studies in *Drosophila* and zebrafish [25,26] have considerably strengthened the idea that altered splicing of a specific gene, or group of genes, vital for motor neuron function may be caused by SMN deficiency, leading to the symptoms of SMA. The splicing of a U12-dependent intron in *Drosophila* stasimon, a transmembrane protein required for sensory–motor circuit formation, is disrupted in a *Drosophila* model of SMA, whereas defects in motor neuron axonal outgrowth caused by morpholino knockdown of SMN in a zebrafish model can be rescued by simultaneous injection of mRNA encoding the human homologue of stasimon. Although the precise function of stasimon is unknown, its sequence suggests that it may have a role in vesicular cargo transport, impairment of which could be particularly damaging in neuronal cells. Interestingly, the key cells damaged by loss of stasimon in *Drosophila* are cholinergic sensory and interneurons, rather than motor neurons. Although this may reflect differences between fly and human nervous systems, it suggests that the search for the key to SMA pathology needs to extend beyond motor neurons themselves.

Does SMN have a distinct role in RNA transport in motor neurons?

The localization of mRNAs to specific regions of the cell and the associated localized synthesis of proteins is a regulatory mechanism observed in many species and in many cell types (reviewed in [27]). Subcellular mRNA localization is particularly pronounced in neural cells and has been implicated in growth cone motility, communication both within and between cells, and synaptic plasticity. Although the localized translation reported in neurons clearly requires mechanisms to transport mRNPs (messenger ribonucleoproteins) along axons and dendrites, there is also increasing evidence that miRNAs (microRNAs) required for translational regulation are also localized to specific regions within neural cells (reviewed in [28]). The mechanistic details of mRNP and miRNA transport and localization within neural cells are far from clear. The potential involvement of SMN in mRNP localization in neurons provides an attractive neuron-specific role for SMN and is supported by several lines of evidence. SMN is seen in dendrites and at axonal branches [29,30] and in growth cones of P19 cells [31]. β-Actin mRNA and protein are mislocalized at the axon tip in motor neurons from severe SMA mice [32], whereas more recent studies have shown that SMN deficiency results in mislocalization of several other mRNAs [33–35]. Highly mobile granules of SMN have been reported in axons of primary neurons by several groups [34,36–39]. Their movement is consistent with motor protein-dependent axonal transport [40]. However, the nature of these granules is not entirely clear. It has been proposed that they are not sites of snRNP assembly as they do not recruit GFP (green fluorescent protein)-tagged SmD1 protein [34] and show no immunoreactivity with the Y12 antibody commonly used to detect members of the Sm protein family [37–39]. There is also some debate as to the extent of SMN granule co-localization with other members of the canonical SMN complex [29,34,37–41], leading to uncertainty about the precise composition and function(s) of these axonal SMN-containing granules. Recent studies also suggest that some of the SMN granules may be associated with COPI (coatomer protein I) vesicle proteins and interact with the Golgi complex [36,42]. What is certainly clear, however, is that SMN has the capacity to interact with a plethora of mRNA-binding proteins (reviewed in [43]), some of which have been shown previously to be components of RNA-transporting granules [44]. Importantly, several of the interactions between SMN and mRNA-binding proteins are impaired by mutations in SMN found in SMA patients [34,35,45,46], leading to the suggestion that SMN may have a role in mRNP assembly analogous to its well-defined role in snRNP assembly.

Evidence for diverse cellular roles for Sm and LSm proteins

Sm and LSm proteins are a diverse family of RNA-binding proteins, capable of forming a variety of heptameric ring structures around numerous small RNAs. For example U7 snRNP, involved in histone pre-mRNA 3′ processing, contains Lsm10 and Lsm11 in place of SmD1 and SmD2 [47,48], whereas U6 snRNP contains a core of LSm2–8 proteins. SMN has been implicated in the assembly of the U7 snRNP Sm/Lsm ring *in vitro* [49], suggesting that SMN may be a more general specificity factor for the assembly of Sm and LSm protein complexes on to small RNAs than originally anticipated. The bacterial protein Hfq is the proposed evolutionary ancestor of the Sm/LSm protein family, acting as a pleiotropic regulator modulating the stability and translation of numerous mRNAs (reviewed in [50]). It is not a surprise therefore to find diverse roles for its descendants in RNA metabolism. Beyond the roles associated with snRNAs, LSm and Sm proteins have also been implicated in control of the localization and turnover of certain mRNAs. LSm proteins 1–7 are required for the degradation of translationally silenced mRNAs within cytoplasmic foci in mammalian cells [51,52]. In a previous study, LSm1 was also demonstrated to be involved in the formation of stable mRNPs in the dendrites of neurons [53]. These LSm1 mRNPs also contain the cap-binding protein CBP80, required for nuclear export of mRNAs, suggesting that they represent newly made mRNAs destined for transport and localized protein synthesis within dendrites as discussed above. Intriguingly, SMN was shown to interact with LSm1 in brain extracts, although it is not clear whether SMN is part of all of the LSm1 complexes in the cytoplasm or just a subset. Further links between the Sm/LSm protein family and mRNP transport come from examination of the mechanism of subcellular localization of the *oskar* mRNP, vital for germline specification and embryonic patterning, in *Drosophila* [54]. Both SmB and SmD3 are part of the *oskar* mRNP and are implicated in its correct localization.

Summary and perspectives

The well-established role for SMN and its associated complex in assembling the Sm protein ring on to snRNAs during splicing snRNP maturation clearly links these proteins in a key event required for pre-mRNA processing. Despite emerging evidence that lowered levels of SMN cause widespread alterations in the snRNP repertoire in cells and in splicing patterns, the molecular mechanism behind SMA remains opaque. The widely documented presence of SMN in highly mobile structures within axons of neural cells and its interaction with numerous mRNA-binding proteins suggests a direct role for SMN in mRNP trafficking that is likely to be of greater importance to cells such as motor neurons, with extremely long axons, than to more compact cell types. The recent documentation of mis-splicing of stasimon in models of SMA certainly provides support for the idea that some specific key transcripts vital for motor neuron function may be mis-spliced. It is interesting in this regard that stasimon is suggested to have a role in vesicular cargo transport, implicating splicing defects in SMA in further compromising trafficking pathways. Add to this the recent suggestions that the Sm and LSm proteins, already intimately linked to the SMN protein, may have more widespread roles in mRNA localization and regulation and a complex picture emerges. The defects in SMA, whether caused at the level of pre-mRNA splicing or mRNP trafficking, appear to converge on pathways of RNA transport that are likely to be of particular importance in cells, such as motor neurons, in which mRNPs need to be localized and regulated at great distances from their site of production in the nucleus.

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