The SMN Complex: An Assembly Machine for RNPs

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In eukaryotic cells, the biogenesis of spliceosomal small nuclear ribonucleoproteins (snRNPs) and likely other RNPs is mediated by an assemblyosome, the survival of motor neurons (SMN) complex. The SMN complex, composed of SMN and the Gemins (2–7), binds to the Sm proteins and to snRNAs and constructs the heptameric rings, the common cores of Sm proteins, on the Sm site (AU₅₋₆G) of the snRNAs. We have determined the specific sequence and structural features of snRNAs for binding to the SMN complex and Sm core assembly. The minimal SMN complex-binding domain in snRNAs (except U1) is composed of an Sm site and a closely adjacent 3' stem-loop. Remarkably, the specific sequence of the stem-loop is not important for SMN complex binding, but it must be located within a short distance of the 3' end of the RNA for an Sm core to assemble. This minimal snRNA-defining "snRNP code" is recognized by the SMN complex, which binds to it directly and with high affinity and assembles the Sm core. The recognition of the snRNAs is provided by Gemin5, a component of the SMN complex that directly binds the snRNP code. Gemin5 is a novel RNA-binding protein that is critical for snRNP biogenesis. Thus, the SMN complex is the identifier, as well as assembler, of the abundant class of snRNAs in cells. The function of the SMN complex, previously unanticipated because RNP biogenesis was believed to occur by self-assembly, confers stringent specificity on otherwise potentially illicit RNA–protein interactions.

RNAs exist in cells as RNPs, complexes of RNAs with RNA-binding proteins (Burd and Dreyfuss 1994; Krecic and Swanson 1999; Yong et al. 2004a). The RNA-binding proteins have essential roles in the biogenesis, function, localization, and stability of the RNAs. There are a very large number of RNA-binding proteins in eukaryotes, and they vary widely in their abundance, RNA-binding specificities, cell-type expression patterns, and biochemical properties. Given the number of cellular RNAs and the vast number of RNA-binding proteins, the problem of formation of specific RNPs is extremely complex. This is particularly important for RNPs that have intricate and highly stable multiprotein structures, exemplified by the spliceosomal snRNPs.

Spliceosomal snRNPs are the major components of the cellular mRNA splicing machinery (Will and Luhrmann 2001; Nilsen 2003). Each snRNP is composed of one or two small nuclear RNAs (snRNAs) bound to a set of RNA-binding proteins. In addition to snRNP-specific proteins, each of the major snRNAs (U1, U2, U4, and U5) is bound to a common set of seven proteins (SmB/B', SmD1, SmD2, SmD3, SmE, SmF, and SmG). These proteins form a seven-membered ring around the short, highly conserved, uridine-rich sequence on each snRNA called the Sm site (Kambach et al. 1999; Achsel et al. 2001; Stark et al. 2001). This Sm core is remarkably stable, resistant to high salt, heparin, and urea (Hamm et al. 1987; Jarmolowski and Mattaj 1993; Raker et al. 1996). Additionally, the conserved seven-nucleotide Sm site sequence (5'-AUUU/CUUG-3') is found in many RNAs. Given the high stability and remarkably slow turnover of these complexes, it is vital that cells only assemble Sm cores on proper snRNAs. Although Sm proteins will self-assemble in vitro in an ATP-independent manner on any RNA that has the short Sm site sequence,

in vivo Sm cores only assemble in an ATP-dependent manner on proper snRNAs (Kleinschmidt et al. 1989; Sumpter et al. 1992; Raker et al. 1996, 1999; Meister et al. 2001a; Pellizzoni et al. 2002a). Self-assembly of Sm cores does not occur in vivo, but rather Sm cores are assembled onto snRNAs by the SMN complex (Fischer et al. 1997; Meister et al. 2001a; Pellizzoni et al. 2002a).

The SMN protein is the product of the spinal muscular atrophy (SMA) disease gene (Lefebvre et al. 1995). Reduction of SMN results in a decreased Sm core assembly and severe motor neuron degeneration in humans (Coovert et al. 1997; Lefebvre et al. 1997; Wan et al. 2005). SMN forms a large, stable complex in the nucleus and cytoplasm of metazoan cells (Liu and Dreyfuss 1996; Paushkin et al. 2002). Besides SMN, the SMN complex contains at least six other proteins known as Gemins2–7 (Fig. 1). SMN oligomerizes via its carboxy-terminal region and is always found tightly associated with Gemin2 (Liu et al. 1997). Gemin3 (also known as DP103 or DDX20) is a DEAD-box RNA helicase (Charroux et al. 1999). Gemin4, a protein of unknown structure and function, associates with the SMN complex via Gemin3 (Charroux et al. 2000). Gemin5 is a multidomain WD-repeat-containing protein (Gubitza et al. 2002). Interestingly, Gemin6 and Gemin7 each contain a domain that has an Sm fold (Baccon et al. 2002; Pellizzoni et al. 2002b; Ma et al. 2005). Recently, another protein of unknown function, Gemin8, has been shown to be part of the SMN complex and interacts directly with Gemin6/7 (Carissimi et al. 2006).

In an ATP-dependent reaction, the SMN complex assembles Sm cores onto the Sm site of each snRNA (Fig. 2) (Fischer et al. 1997; Meister et al. 2001a; Pellizzoni et al. 2002a). snRNAs are transcribed in the nucleus by RNA polymerase II and exported to the cytoplasm for Sm core assembly by the export factor PHAX

Figure 1. The SMN complex is a large, oligomeric multiprotein complex. The SMN complex contains SMN as well as at least six other proteins shown as Gemin2–7. For simplicity, the SMN complex is shown here as a dimer. Shown on the left is a silver stain of the SMN complex purified from HeLa extract. Shown on the right are several proteins that directly interact with the SMN complex, as well as the RNPs in which they function.

(Ohno et al. 2000; Segref et al. 2001). The SMN complex, presumably preloaded with Sm proteins, associates with snRNAs shortly after export and transfers the Sm proteins to the Sm site of the RNA. The 5' cap is then hypermethylated to form the 2,2,7-trimethyl guanosine cap, and the mature snRNP is then imported into the nucleus by snurportin and importin β for final association with the snRNP-specific proteins and utilization in mRNA splicing (Mattaj and De Robertis 1985; Fischer and Luhmann 1990; Fischer et al. 1993; Plessel et al. 1994; Huber et al. 1998).

The SMN complex interacts directly with both the Sm proteins and the snRNA. Each protein of the SMN complex, except Gemin2, directly binds to Sm proteins (Liu et al. 1997; Charroux et al. 1999, 2000; Baccon et al. 2002; Gubitz et al. 2002; Pellizzoni et al. 2002b). The Sm domains of Gemin6 and Gemin7 may bind to Sm proteins by mimicking the conserved Sm–Sm interface (Ma et al. 2005). Additionally, SmB/B', SmD1, and SmD3 contain carboxy-terminal Arg/Gly-rich tails that are methylated by JBP1/PRMT5 in the 20S methylosome complex (Fig. 2) (Brahms et al. 2000, 2001; Friesen et al. 2001b, 2002; Meister et al. 2001b). The SMN protein itself binds via its tudor domain directly to these symmetric dimethyl-arginine tails, and methylation of these proteins enhances Sm protein binding to the SMN complex (Fig. 2) (Friesen et al. 2001a).

Independent of its interaction with Sm proteins, the SMN complex binds directly to snRNAs (Pellizzoni et al. 2002a,b; Yong et al. 2002, 2004b; Golembe et al. 2005a,b;

Battle et al. 2006). The SMN complex performs an essential function in cells by scrutinizing cellular RNAs and ensuring that Sm cores are only assembled onto proper snRNAs (Pellizzoni et al. 2002a). To accomplish this, the SMN complex must be able to recognize specific features of snRNAs in addition to the short Sm site.

HOW DOES THE SMN COMPLEX IDENTIFY snRNAs?

The snRNP Code

Recent work allowed the elucidation of specific sequence and structural features that are recognized by the SMN complex and identified snRNAs for snRNP assembly. Mapping of the minimal SMN complex interacting regions of the major spliceosomal snRNAs (U1, U2, U4, and U5) as well as some of the minor snRNAs (U11) revealed that for each of the snRNAs except U1, the minimal SMN-complex-binding region includes the Sm site, as well as at least one stem-loop immediately 3' of the Sm site (Fig. 3) (Yong et al. 2002, 2004b). In each case, mutation of the Sm site decreases the binding of the SMN complex (Yong et al. 2004b). U1, however, is different, yet still highly specific. The Sm site of U1 is different from, and not functionally interchangeable with, the Sm site of the other snRNAs. The high-affinity SMN-complex-binding site in U1 snRNA maps to the first stem-loop near the 5' end of the molecule (SL1), and point mutations in the loop of SL1 disrupt SMN complex binding (Fig. 3) (Yong et al. 2002).

Figure 2. The snRNP assembly pathway. snRNAs are transcribed in the nucleus by RNA polymerase II, bound by the cap-binding complex (CBC) and the PHAX, and then exported to the cytoplasm. Following export, the snRNAs are bound by the SMN complex preassociated with Sm proteins that have been methylated by the 20S methylosome complex. Following Sm core assembly, 3'-end processing, and cap hypermethylation, the snRNPs are bound by snurportin and imported to the nucleus to Gems and Cajal bodies (CB).

Studies using small snRNAs encoded by *Herpesvirus saimiri* (HSURs) provided additional information that allowed a precise definition of the snRNA-binding specificity of the SMN complex. HSURs are viral RNAs whose functions are currently being investigated (Lee et al. 1988; Lee and Steitz 1990; Cook et al. 2004, 2005). The SMN complex assembles Sm cores on canonical Sm sites contained in each of these RNAs (Golembe et al. 2005b). Since these RNAs are small, contain canonical Sm sites, and are assembled into snRNPs by the SMN complex, they are ideal models for studying the details of the SMN complex–snRNA interaction. The minimal SMN-complex-binding site in each of these snRNAs again includes the Sm site and at least one stem-loop immediately 3' of the Sm site (Fig. 3) (Golembe et al. 2005a). Extensive mutagenesis and phosphothioate interference mapping revealed that the SMN complex recognizes specific nucleotides within the Sm site. Specifically, the SMN complex recognizes the bases of the first adenosine and the first and third uridines of the Sm site (Golembe et al. 2005a). Additionally, the SMN complex senses the phosphate backbone at the positions of the first and third uridines of the Sm site, a profile that is significantly different from that of the Sm protein interaction with these

snRNAs (Golembe et al. 2005a). The SMN complex further requires the presence of the 3' stem-loop, but the specific nucleotide sequence of the stem-loop and its length are not critical (Golembe et al. 2005a). Additionally, alkaline hydrolysis experiments demonstrated that in each case, the SMN complex forms at least one critical interaction with a region 5' of the Sm site (Golembe et al. 2005a).

These data have allowed the determination of specific sequence and structural features that permit the SMN complex to bind an RNA and assemble them into snRNPs. Although purified Sm proteins can assemble in vitro on any RNA that contains a short stretch of uridines, in vivo Sm core assembly only occurs on RNAs that bind to the SMN complex. The SMN complex specifically recognizes the first adenosine and the first and third uridines of the Sm site. The SMN complex absolutely requires the presence of a short 7–12-bp stem-loop, although its sequence is not critical. The SMN complex requires that the 3' end of the snRNA be within a short distance (<14 nucleotides) of the Sm site. Additionally, in all cases, the SMN complex recognizes at least one nucleotide upstream of the Sm site, although this interaction is RNA-specific and can be quite important, as in the case of U1. These features constitute a code that is read by the SMN

Figure 3. The SMN complex binds specific regions of snRNAs. Shown are the secondary structures of several snRNAs. The minimal SMN-complex-binding regions are highlighted in pink and yellow.

complex and determines which cellular RNAs are defined as snRNAs and assembled into snRNPs (Golembe et al. 2005a).

Gemin5 Is the snRNA-binding Protein of the SMN Complex

Several lines of evidence have demonstrated that the SMN complex itself binds snRNAs independent of Sm proteins. First, Sm proteins are readily removed from the SMN complex by simply washing the complex in high-salt buffer (Pellizzoni et al. 2002a,b; Yong et al. 2002, 2004b; Golembe et al. 2005a,b; Battle et al. 2006). These Sm-free SMN complexes fail to assemble Sm cores, but still bind snRNAs with high affinity and specificity. Second, the specificity of the Sm protein–snRNA interaction differs significantly from that of the SMN complex–snRNA interaction (Yong et al. 2002, 2004b; Golembe et al. 2005a). Although purified Sm proteins will bind any RNA containing an Sm site, the SMN complex will only bind and assemble Sm cores on RNAs that contain the additional sequence and structural features described above as the snRNP code (Golembe et al. 2005a). This left the question of which protein of the SMN complex binds and identifies snRNAs.

Gemin5 is an integral component of the SMN complex, associating with SMN in both the cytoplasm and nuclear gems of metazoan cells (Gubitz et al. 2002). Double-labeling immunofluorescence with antibodies against Gemin5 and Sm proteins shows that Gemin5 is mainly dispersed throughout the cytoplasm and concentrated in nuclear gems, whereas the majority of Sm proteins are found as assembled snRNPs in the nucleus (Fig. 4). Gemin5 is the largest component of the SMN complex, with a molecular mass of approximately 175 kD (Gubitz et al. 2002). Gemin5 is a multidomain protein containing no recognizable RNA-binding motifs. The amino-terminal domain contains 13 WD repeats, whereas the entire carboxy-terminal half of Gemin5 shows no significant sequence homology with any other known proteins (Gubitz et al. 2002). Gemin5 efficiently cross-links to snRNAs in cytoplasmic extract (Battle et al. 2006). The cross-linking is specific to snRNAs that bind to the SMN complex, and the cross-linking occurs within the SMN complex (Battle et al. 2006). Purified Gemin5 from HeLa cells, as well as recombinant Gemin5 expressed in *Escherichia coli*, directly binds to snRNAs. In all cases, the specificity of the Gemin5 interaction with snRNA matches the specificity of the full SMN complex for snRNA (Battle et al. 2006).

Figure 4. Immunofluorescence localization of Gemin5 and Sm proteins. Indirect double-labeling immunofluorescence on HeLa cells using anti-Gemin5 (10G11) monoclonal antibody (*A*, red) and anti-Sm (Y12) antibody (*B*, green). Combined image is shown in *C*.

Reduction of Gemin5 by RNA interference (RNAi) reduces both the ability of the SMN complex to bind snRNAs and the ability of the SMN complex to assemble Sm cores on snRNAs (Battle et al. 2006). Gemin5 therefore functions as the critical cellular factor that identifies snRNAs and allows the SMN complex to assemble them into snRNPs.

Although recognition of the snRNP code in an RNA by Gemin5 is required for Sm core assembly, it is not sufficient. Gemin5 will bind to any RNA with a snRNP code, and the position of the code within the RNA is not crucial. For example, Gemin5 will bind to an RNA construct in which the snRNP code is at the 5' end of the molecule and significant random sequence is at the 3' end of the molecule (Fig. 5A). In fact, the full SMN complex will bind these RNAs via Gemin5 (Golembe et al. 2005a; Battle et al. 2006). However, the SMN complex will not assemble Sm cores on an RNA that does not have the 3' end of the RNA close in space to the Sm site (Golembe et al. 2005a). Therefore, something in the SMN complex senses the position of the 3' end of the RNA and ensures that Sm cores are only assembled on snRNAs with proper 3' ends (Fig. 5B).

A Role for the SMN Complex in the Biogenesis of Other RNPs

In addition to direct interactions with the components of snRNPs, snRNA, and Sm proteins, the SMN complex interacts with RNA-binding proteins that are components of other classes of RNPs, and they can therefore be considered as likely substrates of the SMN complex (see Fig. 1). These interactions suggest that the SMN complex has a central role in the biogenesis of diverse RNPs in addition to its role in snRNP biogenesis. For instance, the replication-dependent histone mRNAs are not polyadenylated at their 3' ends, but rather are processed at their 3' ends by the U7 snRNP. The U7 snRNA contains a single-stranded uridine-rich sequence similar to an Sm site (5'-AAUUUGUCUAG-3'). Around this site, a mixed Sm-Lsm core assembles in which Smd1 and Smd2 have been replaced by two other proteins, LSm10 and LSm11. Immunodepletion of the SMN complex from *Xenopus* egg extracts reduced U7 snRNP assembly (Pillai et al. 2003). Gemin5 does not directly interact with the U7

snRNA (Battle et al. 2006); however, the SMN complex has been reported to bind to LSm10 and LSm11 (Pillai et al. 2003; Schumperli and Pillai 2004). It is likely that the SMN complex utilizes its interaction with LSm11 to participate in the assembly of the U7 snRNP.

SMN also binds directly to fibrillarin and GAR1, constituents of box C/D and box H/ACA small nucleolar RNPs (snoRNPs), respectively (Jones et al. 2001; Pellizzoni et al. 2001a). In vitro binding assays performed with full-length and truncated forms of the protein showed that SMN interacts directly with both fibrillarin and GAR1 and that the interactions are mediated by the RG-rich domains of fibrillarin and GAR1. Co-immunoprecipitation experiments demonstrated that the SMN complex interacts with fibrillarin and GAR1 in vivo in human cells (Pellizzoni et al. 2001a). Furthermore, overexpression of a dominant-negative mutant of SMN, SMN Δ N27, causes a massive reorganization of snoRNPs, pointing again to a functional interaction between snoRNPs and the SMN complex in vivo. We observed that snoRNPs are depleted from the nucleolus and accumulate in the SMN Δ N27-containing structures in cells expressing this dominant-negative mutant of SMN. In these cells, transcription is inhibited in both the nucleoplasm and the nucleolus (Pellizzoni et al. 2001b), and the reorganization of snoRNPs may contribute to the inhibition of nucleolar transcription. The snoRNPs are ribonucleoprotein particles very much akin to snRNPs, and these findings therefore argue that the SMN complex very likely also has a role in the biogenesis of snoRNPs.

Another likely function of the SMN complex is suggested by the observation that the SMN complex interacts with RNA helicase A (RHA) (Pellizzoni et al. 2001b). RHA is an ATP-dependent DEAH-box RNA helicase that associates with RNA polymerase II and has been reported to play a part in transcription. Thus, the SMN complex may also have a role in transcription, specifically in the assembly of the major transcription machinery of the cell. In support of this conclusion, the overexpression of SMN Δ N27 mutant leads to the inhibition of transcription in vivo, whereas wild-type SMN leads to stimulation of transcription (Pellizzoni et al. 2001b). In addition, Gemin3 has also been shown to be involved in the regulation of transcription of certain

Figure 5. RNA binding by Gemin5 is necessary but not sufficient for Sm core assembly. (A) Gemin5 binds to an RNA containing a snRNP code derived from HSUR5 snRNA at the 5' end of the RNA. Direct RNA-binding assay with Gemin5 and 32 P-labeled HSUR5 minimal SMN-complex-binding RNA or the same RNA with additional 70 nucleotides at the 3' end was performed as described previously (Battle et al. 2006). (B) Gemin5 and the full SMN complex bind to RNAs containing a snRNP code followed by a long 3' extension, but the SMN complex will only assemble Sm cores on snRNAs that have the 3' end near the Sm site.

reporter genes by RNA polymerase II (Campbell et al. 2000; Yan et al. 2003). However, the mechanism by which SMN and its interacting partners act in these processes remains unknown.

CONCLUSION

The SMN complex has an essential role as an assemblyosome in snRNP biogenesis. This function was unexpected because RNPs in general, and Sm cores in particular, can readily form in vitro from purified Sm proteins and snRNA. In the cell, however, the potential for inaccurate Sm core assembly necessitates a specificity factor to ensure correct RNPs are formed, a function performed in eukaryotes by the SMN complex. What emerged from recent studies is the remarkable capacity of the SMN complex to identify, through Gemin5, specific RNAs as snRNAs and assemble them into snRNPs. Future studies on the functions and structure of the SMN complex should lead to a detailed picture of its mechanism of action and a better understanding of the molecular basis of SMA, and it

should pave the way for the development of therapeutic approaches to this devastating disease.

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