11

The Lsm Proteins: Ring Architectures for RNA Capture

Jens M. Moll, Meghna Sobti[1] and Bridget C. Mabbutt
Department of Chemistry and Biomolecular Sciences, Macquarie University, Australia

1. Introduction

It is today recognized that the vast majority of the cellular pool of RNA (nearly 98% in humans) comprises non-coding RNA (ncRNA) species (Mattick, 2001), with only a small proportion serving as direct template for protein synthesis. The diverse ncRNA forms are themselves capable of function, involved in a plethora of tasks such as protein scaffolding, *cis* and *trans* regulatory roles and catalysis (Lilley, 2005; Mattick & Makunin, 2006). Many of these functions are carried out in tight partnership with specific ancillary proteins within large ribonucleo-protein complexes (RNPs) (Eddy, 2001).

Various types of ncRNA, as well as RNPs containing tRNA, rRNA or snRNA, directly interact with mRNA at different stages of its life. Figure 1 presents an overview of the maturation of pre-mRNA and the fate of the mRNA generated. Pre-mRNA initially undergoes modification to enhance its stability: a 5′ methyl guanosine (m_7G) cap added during transcription (Wen & Shatkin, 1999) and a poly(A)-tail placed in the 3′ region by the polyadenylation machinery (Proudfoot et al., 2002; Balbo & Bohm, 2007). Following initiation of spliceosomal assembly by recruitment of core particles in the cytoplasm, non-coding introns are spliced from the pre-mRNA sequence by the mature spliceosome in the nucleus (Crick, 1979; Pozzoli et al., 2002). This multi-megadalton complex itself contains 170 protein components and various types of snRNA, rivaling the ribosome in molecular complexity (Wahl et al., 2009).

Within the spliceosome, several distinct small nuclear RNP (snRNP) core complexes each contain snRNA organized around specific ring-structured protein assemblies. For those known as U1-, U2-, U4- and U5-snRNPs, these ring scaffolds are provided by members of the Sm protein family (Luhrmann et al., 1990), recruited to their specific snRNA partners in the cytoplasm at a distinct Sm-site of bases (Urlaub et al., 2001; Peng & Gallwitz 2004). The core snRNPs are reimported into the nucleus for further processing and spliceosome assembly (Will & Luhrmann, 2001; Patel & Bellini 2008). In contrast, U6 snRNA is first modified within the nucleoli and then engages with a related protein ring, in this case containing Lsm ("Sm-like") proteins Lsm2-Lsm8. Together with the U1-U5 particles, the U6 snRNP is translocated to Cajal bodies for formation of the U4/U6*U5 tri-snRNP (Patel & Bellini, 2008). The mature snRNPs eventually assemble on pre-mRNA for intron removal steps (Will & Luhrmann, 2001; Patel & Bellini 2008).

[1] Present address: Structural and Computational Biology Division, Victor Chang Cardiac Research Institute, Australia

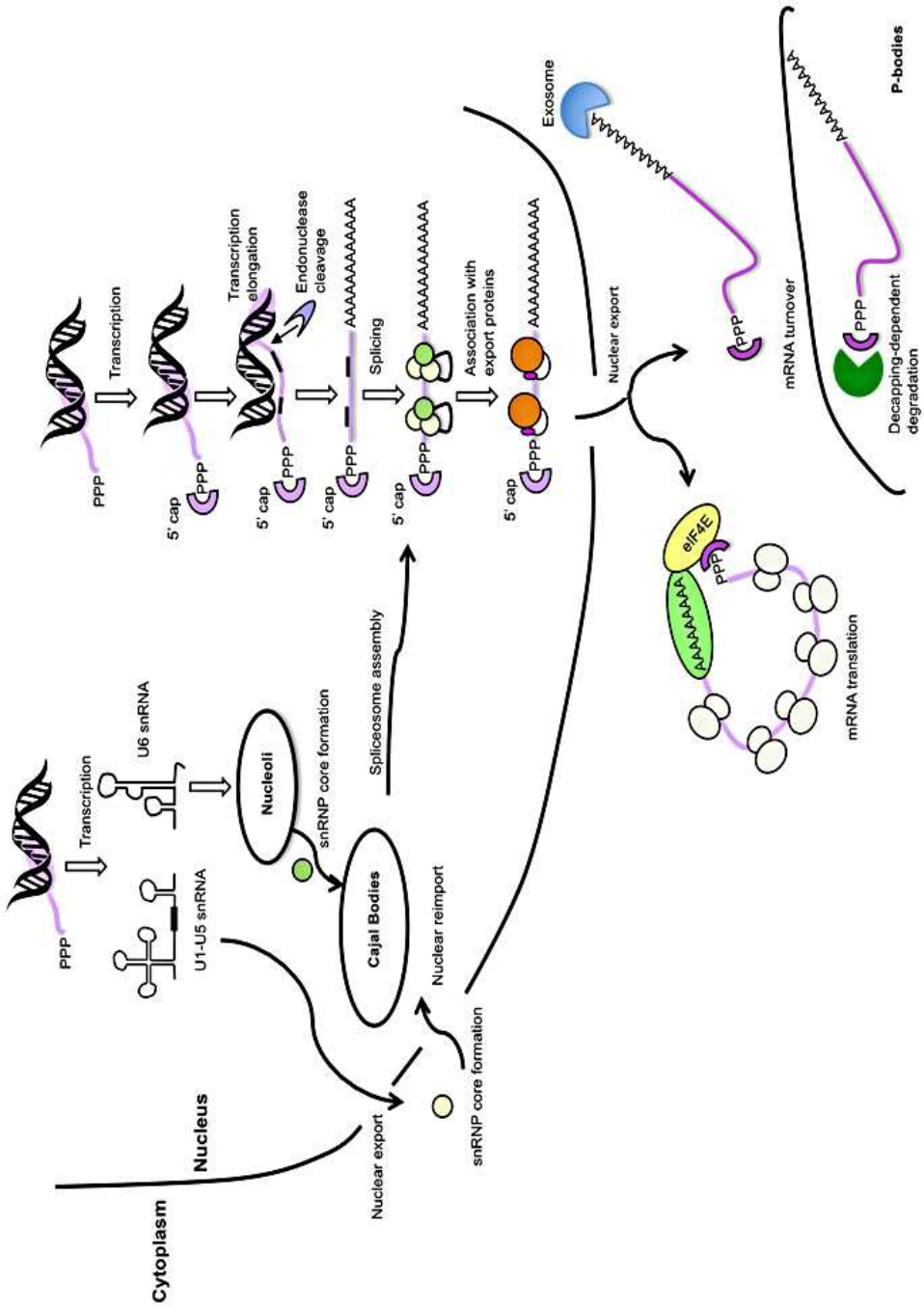


Fig. 1. Lifecycle of mRNA from transcription to decay.

Following excision of introns, mRNA enters the cytoplasm via the nuclear pore complex to be either translated or degraded. In eukaryotes, two pathways are utilized for mRNA decay: i) 3′-to-5′ degradation by the exosome or ii) 5′-decapping, followed by 5′-to-3′ exonuclease degradation (Garneau et al., 2007). In either event, decay is initiated by shortening of the poly(A)-tail by deadenylases (Tucker et al., 2001; Garneau et al., 2007; Nissan et al., 2010). Protein machinery required for the 5′-decapping pathway is found enriched in cytoplasmic foci known as processing or P-bodies (Sheth & Parker 2003), which appear to control the sorting and storage of mRNA. Within P-bodies, a specific assembly of Lsm proteins (Lsm1-Lsm7) and ancilliary protein factors expedites mRNA decapping and subsequent breakdown by ribonuclease (Nissan et al., 2010). While the extent to which mRNA decay is restricted to P-bodies is unclear, sequestered mRNA species are observed to leave P-bodies and may re-enter translation (Brengues et al., 2005).

2. Phylogeny of Lsm protein sequences

The Lsm proteins recur as molecular chaperones for RNA during the many steps of its processing, sorting and regulation (Beggs, 2005). While Sm proteins were first found enriched in a patient with systemic lupus erythematosis (Lerner & Steitz 1979), the wider protein family has since been described across all domains of life (Beggs, 2005; Ma et al., 2005). Members include eukaryotic Lsm (Salgado-Garrido et al., 1999), Sm (Kambach et al., 1999) and SMN/Gemin proteins (Selenko et al., 2001; Ma et al., 2005), archaeal Lsm proteins (Collins et al., 2001), the bacterial protein Hfq (Schumacher et al., 2002) and a recently identified Lsm homolog of cyanophage origin (Das et al., 2009). Eukaryotic genomes can contain up to 16 Lsm and 7 Sm proteins (Albrecht & Lengauer 2004), yet 2-3 Lsm proteins are generally encoded in archaea (Collins et al., 2001; Toro et al., 2002; Mura et al., 2003) and only a single form is evident in bacteria and cyanophage (Schumacher et al., 2002; Das et al., 2009).

A characteristic feature of the Lsm proteins is their natural tendency to form ring-shaped quaternary complexes, each of a precise composition related to cellular location and RNA target (Beggs, 2005; Spiller et al., 2007). In prokaryotes and archaea, homomeric complexes of six or seven Lsm protomers appear to be functional, whilst discrete heteromeric assemblies of seven distinct Lsm proteins are found in eukaryotes. The individual Lsm proteins vary in size from 8-25 kDa (78-240 amino acids); representative sequences are depicted in Figure 2. Within each, a bipartite consensus sequence (designated Sm1 and Sm2 motifs) can be identified. These motifs arise from strands β1-β3 and β4-β5 of the core β-sheet structure, respectively. A variable stretch of residues between these conserved segments is created by a surface-exposed interconnecting loop (Kambach et al., 1999; Collins et al., 2001). The N- and C-terminal tail regions of each Lsm sequence are often highly charged and differ markedly between members; these are considered to provide contact points for additional protein or RNA interactions (Reijns et al., 2008; Reijns et al., 2009; Weber et al., 2010). In the case of the eukaryotic Lsm1 and Lsm4 proteins, these tail segments are notably elongated.

The most highly conserved sequence segments across the Lsm family include specific amino acid sidechains implicated in RNA-binding. These are localized to two specific loop features, as outlined in Figure 2. For archaeal and eukaryotic Lsm proteins, sequence motifs Asp-x-ϕ-ϕ-Asn (ϕ = hydrophobic) and Arg-Gly-(Asp) (Kambach et al., 1999; Collins et al., 2001; Toro et al., 2001) are characteristic of loops L3 and L5, respectively. In bacterial Hfq, these RNA-binding segments occur as Asp-x-ϕ-ϕ-ϕ (L3) and Tyr-Lys-His (L5) (Schumacher

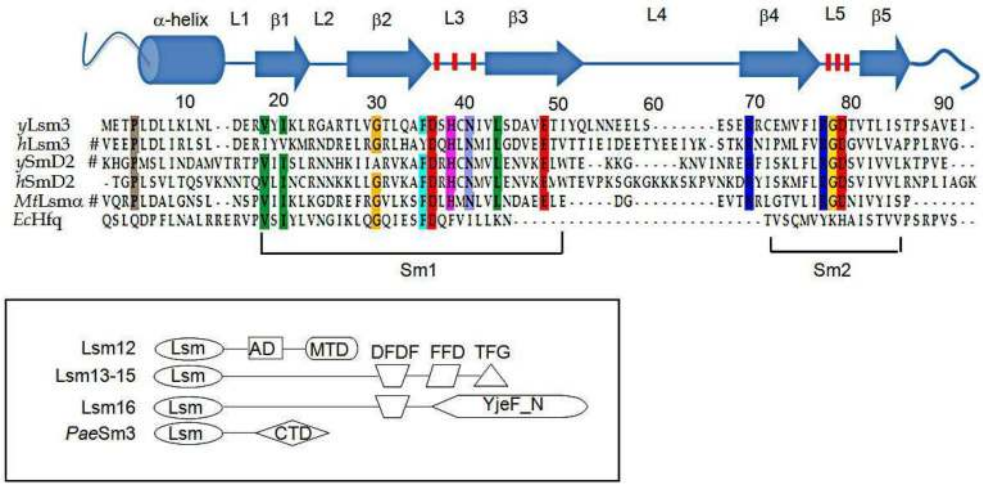


Fig. 2. Structure-based Lsm protein sequence alignment. Sequences displayed are for *S. cerevisiae* Lsm3 (*y*Lsm3), *H. sapiens* Lsm3 (*h*Lsm3), *S. cerevisiae* SmD2 (*y*SmD2), human SmD2 (*h*SmD2), *M. thermoautotrophicum* Lsmα (*Mt*Lsmα) and *E. coli* Hfq (*Ec*Hfq). Shaded residues represent areas with ≥ 80% sequence homology. Secondary structure assignment is based on the crystal structure of *y*Lsm3 (Naidoo et al., 2008). Red bars indicate conserved residues implicated in RNA binding. # indicates additional truncated residues not displayed. Boxed insert shows organization of other Lsm multidomain proteins: AD, anticodon binding domain; MTD, methyl transferase domain; DFDF, DFDF-x(7)-F containing domain; FFD, Y-x-K-x(3)-FFD-x-(IL)-S containing motif; TFG: [RKH]-x(2-5)-E-x(0-2)-[RK]-x(3-4)-[DE]-TFG containing domain. CTD, C-terminal domain2.

et al., 2002). For this bacterial ortholog, a highly conserved Gln residue on the N-terminal α-helix is also implicated in RNA-binding (Schumacher et al., 2002).

Overall, the bacterial protein Hfq shows little sequence conservation with its archaeal and eukaryotic orthologs, yet the archaeal and eukaryotic Lsm proteins share some limited sequence similarity (>20 %). The following Lsm-Sm protein paralogs are identifiable: Lsm1-SmB, Lsm2-SmD1, Lsm3-SmD2, Lsm4-SmD3, Lsm5-SmE, Lsm6-SmF, Lsm7-SmG, Lsm8-SmB (Fromont-Racine et al., 2000). These specific sequence relationships suggest the eukaryotic Lsm proteins to have evolved from a common archaeal ancestor in two waves (Khusial et al., 2005; Veretnik et al., 2009). A first gene duplication event likely created eight distinct Lsm proteins, from which later evolved the Sm protein group. The diversity of biological activities of Lsm proteins compared to their more specialized Sm counterparts supports this two-step evolution model (Beggs, 2005; Khusial et al., 2005). The presence of up to three Lsm proteins in archaea, as well as an Hfq-like protein in archaeal *M. jannaschii*, further supports a common ancestor of eukaryotic and archaeal Lsm proteins (Fischer et al., 2011).

A few multidomain proteins incorporating Lsm components have been observed (summarized, Figure 2). Lsm12 includes t-RNA and methyltransferase domains (Albrecht & Lengauer, 2004), and Lsm13, Lsm14 and Lsm15 all contain a central DFDF-x(7)-F domain (Albrecht & Lengauer, 2004; Anantharaman & Aravind, 2004). Lsm16 features a remarkably disrupted Lsm variant (lacking both the N-terminal α-helix and a complete β4 strand) in addition to FDF and YjeF-N domains (Albrecht & Lengauer, 2004; Tritschler et al., 2007). This protein is suggested to be dimeric in solution (Ling et al., 2008). The archaeal protein Pa-Sm3 contains an Lsm-like domain in addition to a C-terminal domain of unknown function adopting an α/β-fold (Mura et al., 2003).

3. Structures of Lsm protein ring complexes

Crystal structures of Lsm and Sm proteins from diverse sources today provide many high-resolution views of the ring morphology of their assemblies. As shown in Figure 3, Lsm rings have been observed to range 58-75 Å in diameter and to contain a central pore of 6-15 Å. Some crystal structures solved to date (Table 1) have been obtained in the presence of specific RNA partners. The recent solving of the human U1-snRNP structures containing the Sm assembly bound together with U1 snRNA and proteins U1-70K and U1-A have been significant and exciting advances (Pomeranz Krummel et al., 2009; Weber et al., 2010). These provide the first molecular detail of L/Sm rings bound to the highly intertwined protein-RNA network within RNP complexes.

Within the various Lsm ring assemblies, each protomer occurs as a highly bent five-stranded antiparallel β-sheet overlaid in most cases by an N-terminal α-helix (Figure 4A). The pronounced twist of the β-sheet aligns strand β5 against β1, so forming an SH3-type barrel loosely related to the OB-fold (Kambach et al., 1999; Collins et al. 2001). Strands β4 and β5 each present on opposite ends of the module, so providing interaction sites for adjacent Lsm subunits via β4-β5′ pairing (Figure 4). Stacking of five to eight protomers in such a manner ultimately results in the formation of the toroid assembly characteristic of all Lsm assemblies (Figure 4).

Within this ring organisation, the N-terminal amphipathic α-helices of each Lsm component are gathered across one face of the toroid, from which also project the unstructured N- and

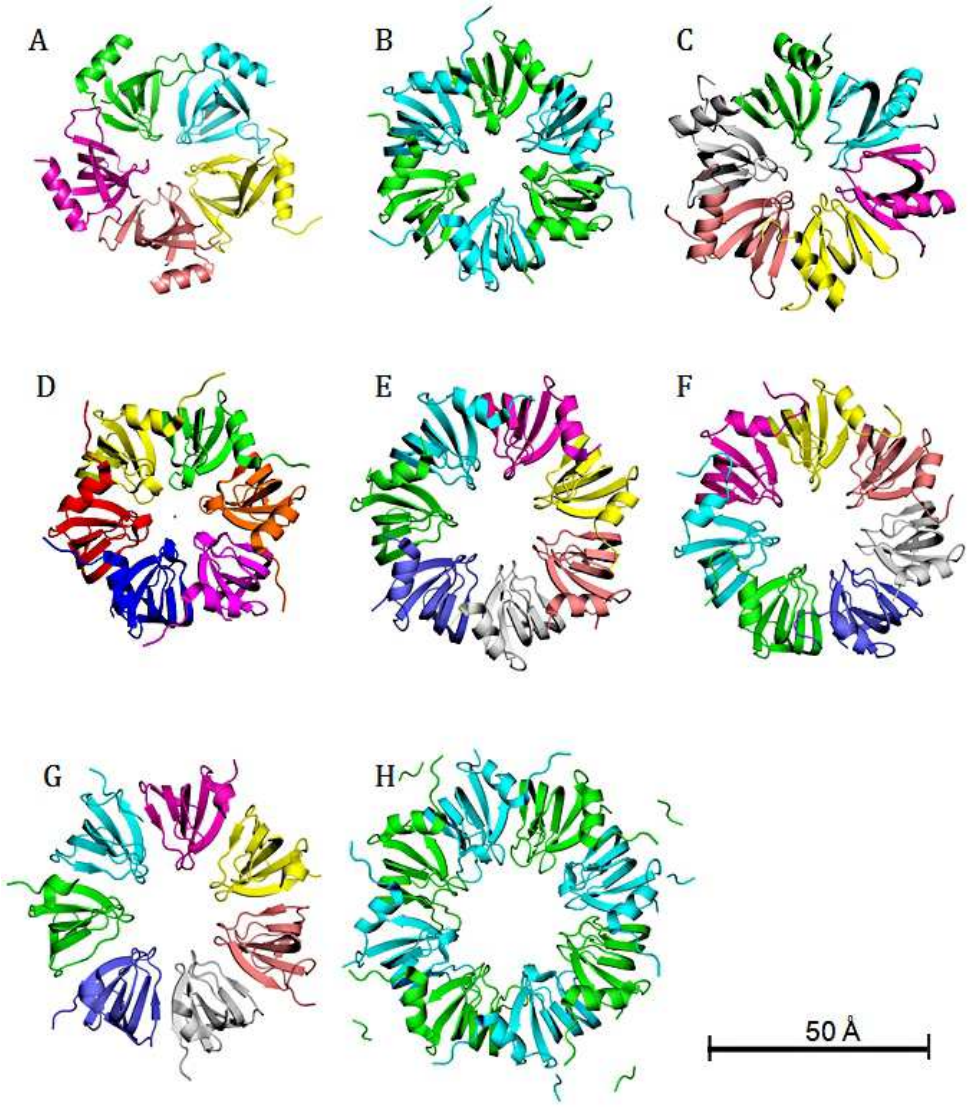


Fig. 3. Selected crystal structures solved for Lsm assemblies. A) Pentamer, cyanophage ECX21941 (PDB 3BY7) 60 Å ring, 9 Å pore. B) Hexamer, of *C. parvum* Lsm5 (PDB 3PGG) 60 Å ring, 10 Å pore. C) Hexamer, *S. aureus* Hfq (PDB 1KQ1) 65 Å ring, 11 Å pore. D) Hexamer, *A. fulgidus* Sm2 (PDB 1LJO) 58 Å ring, 6 Å pore. E) Hexamer, *A. fulgidus* Sm2 (PDB 1LJO) 58 Å ring, 6 Å pore. F) Heptamer, *A. fulgidus* Sm1 (PDB 1I4K) 65 Å ring, 13 Å pore. G) Heptamer, *M. thermoautotrophicum* Lsmα (PDB 1I81) 65 Å ring, 10-15 Å pore. F) Heptamer, *S. cerevisiae* Sm-F (PDB 1N9R) 65 Å ring, 10-15 Å pore. H) Octamer, *S. cerevisiae* Lsm3 (PDB 3BW1) 75 Å ring, 15 Å pore.

	Protein[1]	PDB ID	Resolution (Å)	Organism	Reference
Hexameric	*Hs*SmD3B	1D3B	2.00	*H. sapiens*	Kambach et al., 1999
	*Sa*Hfq	1KQ1	1.55	*S. aureus*	Schumacher et al., 2002
	*Sa*Hfq*	1KQ2	2.71	*S. aureus*	Schumacher et al., 2002
	*Af*Sm2	1LJO	1.95	*A. fulgidus*	Toro et al., 2002
	*Ec*Hfq	1HK9	2.15	*E. coli*	Sauter et al., 2003
	*Pa*Hfq	1U1S	1.60	*P. aeruginosa*	Nikulin et al., 2003
	*Pa*Hfq	1U1T	1.90	*P. aeruginosa*	Nikulin et al., 2003
	*Mj*Sm	2QTX	2.50	*M. jannaschii*	Nielsen et al., 2007
	*Cp*Lsm5	3PGG	2.14	*C. parvum*	Vedadi et al., 2007
	*A*Hfq	3HFN	2.31	*Anabena sp.*	Boggild et al., 2009
	*Ec*Hfq*	3GIB	2.40	*E. coli*	Link et al., 2009
	*S*Hfq	3HFO	1.30	*Synchocystis sp.*	Boggild et al., 2009
	*Pa*H57THfq	3INZ	1.70	*P. aeruginosa*	Moskaleva et al., 2010
	*Pa*H57AHfq	3M4G	2.05	*P. aeruginosa*	Moskaleva et al., 2010
	*Bs*Hfq	3HSB	2.20	*B. subtilis*	Someya et al., 2010[3]
Heptameric	*Mt*Lsmα	1I81, 1MGQ	2.00, 1.70	*M. thermoautotrophicum*	Collins et al., 2001
	*Pae*Sm1	1I8F	1.75	*P. aerophilum*	Mura et al., 2001
	*Af*Sm1	1I4K	2.50	*A. fulgidus*	Toro et al., 2001
	*Af*Sm1*	1I5L	2.75	*A. fulgidus*	Toro et al., 2001
	*Mt*Lsmα	1JBM	1.85	*M. thermoautotrophicum*	Mura et al., 2003b
	*Pae*Sm1	1JRI	1.75	*P. aerophilum*	Mura et al., 2003b
	*Pae*Sm1	1LNX	2.05	*P. aerophilum*	Mura et al., 2003b
	*Pab*Sm1	1H64	1.90	*P. abysii*	Thore et al., 2003
	*Pab*Sm1*	1M8V	2.60	*P. abysii*	Thore et al., 2003
	*Pae*Sm3	1M5Q	2.00	*P. aerophilum*	Mura et al., 2003a
	*Pae*Sm1	1LOJ	1.90	*M. thermoautotrophicum*	Mura et al., 2003b
	*Sc*SmF	1N9R	2.80	*S. cerevisiae*	Collins et al., 2003
	*Sc*SmF	1N9S	3.50	*S. cerevisiae*	Collins et al., 2003
	*Ss*Sm1	1TH7	1.68	*S. solfataricus*	Kilic et al., 2005
	U1-snRNP*	3CW1	5.49	*H. sapiens*	Pomeranz Krummel et al., 2009
	U1-snRNP*	3PGW	4.40	*H. sapiens*	Weber et al., 2010
Other	*Cph*Lsm	3BY7	2.60	*Cyanophage*	Das et al., 2009
	*Sc*Lsm3	3BW1	2.50	*S. cerevisiae*	Naidoo et al., 2008
	*Pfu*Q8TZN2[2]	1YCY	2.80	*P. furiosus*	Huang et al., 2004[3]

[1]Proteins are named by the first letters of the species, followed by the type of protein. Asterisked entries indicate structures solved in the presence of RNA.
[2]Hypothetical protein adopting an Lsm fold.
[3]Structure deposited without supporting publication.

Table 1. Crystal structures solved for Lsm assemblies (to 2010)

C-terminal extensions. The opposite face of the ring, named the distal face, is predominantly composed of residues of the variable loop L4 segments. All the Lsm ring structures (across eukarya, archaea and bacteria) reveal clusters of positive residues lining the internal pore, as well as pronounced positive elements on the distal face (Toro et al., 2001; Brennan & Link, 2007; Naidoo et al., 2008).

The body of structural data adds to biochemical understanding concerning L/Sm-RNA interactions, and distinct RNA sites within the protein oligomer. These include i) a binding site within the lumen of the ring, ii) an external contact site on the helix face and iii) residues located on the distal face of the complex (Figure 4). The first of these sites engages residues from loops L3 and L5, contributed from all Lsm components to create a nucleotide-binding pocket running around the inner rim (Weber et al., 2010). The specific architecture and repeated circular location of these specific, highly conserved, sidechains enables one nucleotide base to be bound per L/Sm protomer. Crystal structures of archaeal and bacterial Lsm complexed with RNA clearly show the oligonucleotides to be threaded around this rim of the toroid (Toro et al., 2001; Schumacher et al., 2002). Each binding "slot" allows specific base stacking to a hydrophobic sidechain of loop L3, as well as contact with the signature Arg residues of loop L5 and H-bonding with Asn residues (strand β4). Further electrostatic contacts (involving conserved Asp (strand β2), Arg (loop L5) and Gly (loop L5) residues) enhance the stability of the Lsm-RNA complex (Toro et al., 2001). Figure 5 displays these relevant binding interactions for U_5 within the lumen site of archaeal *Af*Sm1.

An external contact site for RNA at the helix face of the Lsm toroid (site ii) is suggested by the crystal structure of *Pa*Sm1 bound with U_7 oligonucleotide (Thore et al. 2003). In this case, each of two sandwiched Lsm rings engage two nucleotides at the N-terminal α-helix (Arg, His) and strands β2 (Tyr) via base stacking and H-bonding.

A third distinct RNA-binding site (iii) is likely to be unique to the bacterial Hfq assembly, and its tripartite form has been detailed in the crystal structure of Hfq bound to poly(A) RNA (Link *et al.* 2009). The protein Hfq engages poly(A) sequences on its distal face via specific residues exposed from strands β2 and β4. There is, however, no evidence for poly(A) binding by eukaryotic Lsm proteins. In the structure of the Hfq/RNA complex, RNA contacts include electrostatic interactions from Lys (strand β2) and Gln (strand β4) sidechains, as well as stacking of bases between Tyr, Leu (strand β2) and Leu and Ile (strand β2′) of adjacent subunits. It is in this region of the toroid that sequence variability of the loop L4 across the Lsm family results in non-conservation of distal face chemistry, so explaining the unique binding properties of Hfq.

Within the crystal structures of the human U1-snRNP complex, multiple RNA interactions made by the ring of Sm proteins include binding sites i) and ii) outlined above (Weber et al., 2010). However, the U1-snRNP structure also clearly demonstrates the role of the Sm sequence extensions and loop regions as additional interaction sites, particularly the C-terminal extensions of SmD3 and SmB. In the lumen of the toroid (i.e. site i), snRNA threads to stack single nucleotides of the Sm site against the key loop L3 and L5 residues, noteably the aromatic sidechains. From the helix face of the ring are projected residues of the N-terminal α-helix and loop L3 of SmD2, forming an external contact site (reminiscent of site ii) that guides the snRNA into the ring pore. Residues from the loop L2 regions of SmD1 and SmD2 appear to guide RNA out from the Sm ring. Protruding beyond the distal face, residues of the elongated L4 loops of SmD2 and SmB provide another important interaction point to clamp and secure a stem-loop of the snRNA.

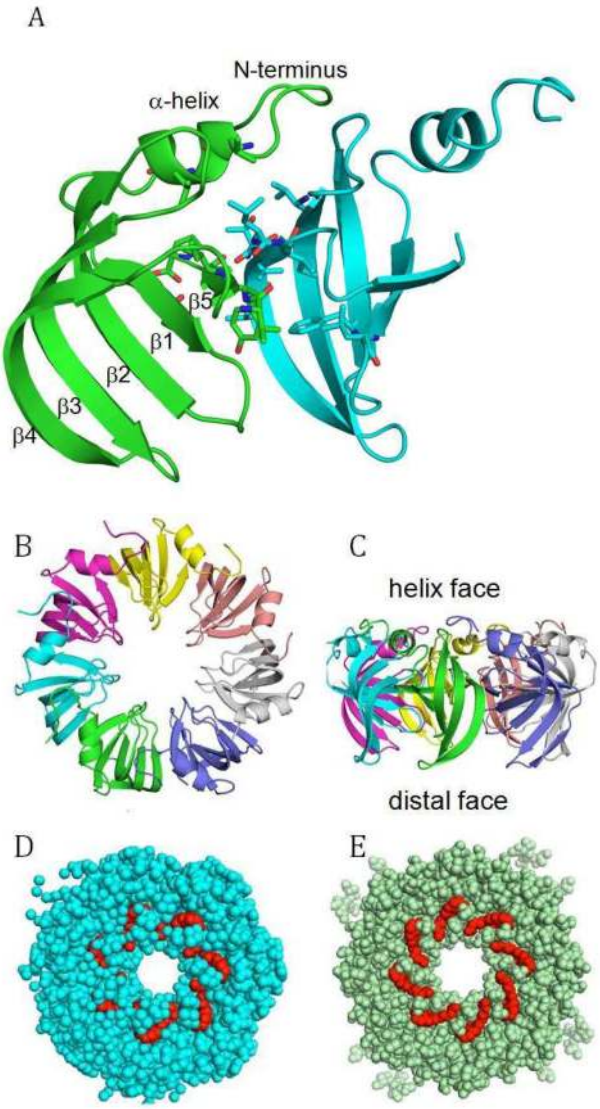


Fig. 4. Lsm fold and quaternary structure. Ribbon diagrams of *Mt*Lsmα (A, B; PDB 1I81) are displayed. A) Dimer interface of *Mt*Lsmα. Chain A is represented in green, chain B in blue. Residues involved in hydrophobic packing at the dimer interface (Chain A: Ile27, Val77, Tyr78 of chain A; Chain B: Leu 30, Phe36, Leu66, Val69, Ile71) are shown in stick representation. B-C) Top and side view of heptameric *Mt*Lsmα. D) Homo-heptameric *Mt*Lsmα (PDB 1I81). E) Homo-octameric yeast Lsm3 (PDB 3BW1). Space-filled models highlight in red conserved residues implicated in RNA binding: Asp in β2, Asn in L3, Arg and Gly in L5.

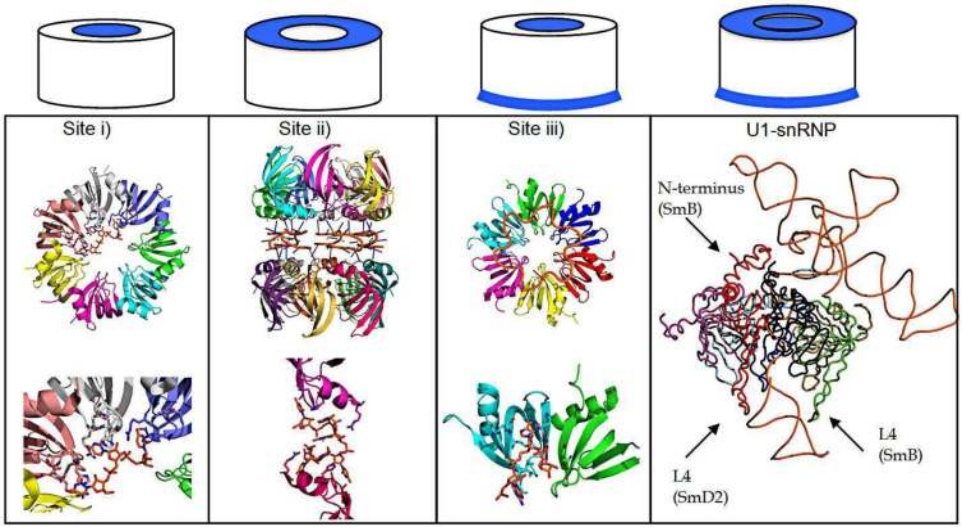


Fig. 5. Three general sites for RNA binding within specific examples of Lsm complexes. Site i) *Af*Sm1 (PDB 1I5L) bound to U_5 RNA viewed from helix face. Site ii) Two *Pa*Sm1 (PDB 1M8V) heptamers are bridged by uridine heptamer. Site iii) *Ec*Hfq (PDB 3GIB) bound to poly(A) viewed from distal face. U1-snRNP) Figure includes side view of the Sm-core of the human U1 snRNP structure (PDB 3PGW).

The majority of crystal structures of Lsm obtained to date portray the hexa- and heptameric protein assemblies that correspond to fully functional homomeric or heteromeric protein groupings. It is, for instance, assumed that complexes of SmD1-SmD2, SmD3-SmB and SmE-SmF-SmG can exist independently in the cytoplasm, yet rearrange into mixed heptamers in the presence of RNA during snRNP formation (Peng & Gallwitz, 2004). However, a few crystal structures suggest that other compositions, e.g. pentamers and octamers, may be stable for eukaryotic Lsm (Naidoo et al., 2008; Das et al., 2009). While it is currently not clear if these organizations are peculiar to recombinant preparations of the Lsm family, they suggest possibilities for a variety of multimeric assemblies *in vivo*. Our own interaction studies indicate that Lsm assemblies may be relatively dynamic in solution, providing capacity to engage in alternative protein partnerships and stable groupings (Sobti et al., 2010).

4. Functional roles for Lsm proteins

Sm and Lsm proteins are known to interact with a diversity of RNA partner species. Specific RNA sequences recognized by various Lsm complexes include the Sm-site (A_2U_5GA) (Raker et al., 1999) and U-rich stretches at the 3′ end of oligoadenylated mRNA (Chowdhury et al., 2007) and RNA polymerase III transcripts, including snRNA (Achsel et al., 1999). Other binding partners include snoRNA (Kufel et al., 2003a), P RNA (Kufel et al., 2002), tRNA (Kufel et al., 2002) and rRNA (Kufel et al., 2003b). Depletion of Lsm proteins 2-5 and 8 in yeast results in defects in post-transcriptional processing of tRNA, P RNA, rRNA, snoRNA and snRNA precursors (Kufel et al., 2002; Kufel et al., 2003b; Kufel et al., 2003a). Yet only minor (or no) effects are observed on depletion of Lsm6 and Lsm7. A summary of some specific Lsm-ncRNA interactions is presented in Table 2.

The Lsm2-Lsm8 complex plays a key role in U6 snRNA maturation, so impacting on the formation of spliceosomal snRNPs (Karaduman et al., 2006). U6 snRNA is the most conserved of all snRNA species and key to the catalytic activity of the spliceosome (Brow, 2002). Newly transcribed U6 pre-snRNA is targeted to the nucleoli following binding of the La protein (Lhp1 in yeast) at its U-rich 3′ region (Wolin & Cedervall, 2002). Following cyclic phosphorylation, La (or Lhp1) is displaced from the U6 snRNA by the Lsm2-Lsm8 assembly (Achsel et al., 1999; Licht et al., 2008), which induces conformational changes that stimulate binding of a recycling factor (p110 or Prp24) (Rader & Guthrie, 2002; Ryan et al., 2002; Karaduman et al., 2006). These conformational changes have been suggested to assist in the formation and recycling of the U4/U6 di-snRNP by exposing single stranded nucleotides for base pairing (Beggs, 2005; Karaduman et al., 2006; Karaduman et al., 2008). The Lsm2-Lsm8 complex is also implicated in decapping steps of mRNA in the nucleus. This was suggested by the finding that Lsm6 and Lsm8 were required for nuclear mRNA decay (Kufel et al., 2004).

A specific role for Lsm1-Lsm7 concerns activation of mRNA decay in P-bodies; depletion of individual yeast Lsm proteins results in the accumulation of capped, oligoadenylated mRNA transcripts (Boeck et al., 1998; Bonnerot et al., 2000; Bouveret et al., 2000; Tharun et al., 2000). This specific Lsm complex is recruited alongside other decay factors to U-rich tracts by the protein Pat1, after its displacement of cap-binding translation factors (Parker & Sheth, 2007). It is likely that Pat1 and Lsm1-Lsm7 are then involved in subsequent activation of the Dcp1-Dcp2 enzyme (Nissan et al., 2010). A variety of studies have demonstrated the interaction of Lsm1-Lsm7 with decapping factors and exoribonuclease Xrn1 (Bonnerot et al., 2000; Bouveret et al., 2000; Tharun et al., 2000; Coller et al., 2001).

RNA species	Lsm function	Selected experimental evidence	References
snRNA	assembly, processing	Lsm2-8 binds 3′ end of U6 snRNA	Achsel et al., 1999
		Lsm2-8 initiates structural rearrangements of U6 snRNA	Karaduman et al., 2006; 2008
		Depletion of Lsm2-Lsm8 results in splicing defects	Mayes et al., 1999
		Splicing activity recovered through recombinant Lsm proteins	Verdone et al., 2004
	and nuclear localization	Lsm2-8 localizes U6 snRNA to the nucleus	Spiller et al., 2007
tRNA	splicing, 3′ and 5′ end-processing	Accumulation of unprocessed pre-tRNA and reduced La/Lhp1 binding upon Lsm2-Lsm5 and Lsm8 depletion	Kufel et al., 2002
		Direct interaction of Lsm3 with tRNA and its splicing factors	Fromont-Racine et al., 1997
P RNA	chaperone	Depletion of Lsm2-Lsm5 and Lsm8 reduces pre-PRNA levels	Mayes et al., 1999
		Reduced La/Lhp1 binding upon Lsm2-Lsm5 and Lsm8 depletion	Kufel et al., 2002
		Lsm2-Lsm7 proteins coprecipitate with pre-PRNA	Salgado-Garrido et al., 1999
rRNA	3′ and 5′ end-processing	Depletion of Lsm2-Lsm5 and Lsm8 delays pre-rRNA processing and increases rRNA decay rate	Kufel et al., 2003b
		Pre-rRNA coprecipitates with Lsm3 but not Lsm1	Kufel et al., 2003b
		Deletion of Lsm6 and Lsm7 genes impairs 20S pre-rRNA processing	Li et al., 2009
snoRNA	3′ end-processing	Lsm2-Lsm5 and Lsm8 depletion results in U3-snoRNA degradation and loss of its 3′ extended precursor	Kufel et al., 2003a
		Reduced La/Lhp1 binding upon Lsm3 or Lsm5 depletion	Kufel et al., 2003a
		Lsm2-Lsm7 but not Lsm1 or Lsm8 coprecipitate with snR5 snoRNA	Fernandez et al., 2004
		Lsm2-4 and 6-8 but not Lsm5 coprecipitate with U8 snoRNA	Tomasevic & Peculis, 2002

Table 2. Lsm binding interactions with ncRNA

In contrast to its enhancement of mRNA decay, however, the Lsm1-Lsm7 complex can also protect mRNA against 3′ end trimming (He & Parker, 2001). This may involve steric hindrance of nuclease attack at mRNA locations on which Lsm1-Lsm7 and Pat1 proteins are bound.

5. Specific functions of bacterial Hfq

Bacterial Hfq is observed to interact with bacterial sRNA and so promote the formation of sRNA-mRNA complexes (Wassarman et al., 2001; Gottesman & Storz, 2010). Bacterial sRNAs are small non-coding RNA species (50-500 nucleotides), which regulate gene expression via base pairing with mRNA transcripts in a similar mechanism to eukaryotic siRNA or miRNA (Storz et al., 2004; Majdalani et al., 2005; Livny & Waldor, 2007; Gottesman & Storz, 2010). Hfq controls gene expression either by rearranging the RNA secondary structure, or by increasing the concentration of RNA locally to promote RNA-RNA interactions (Moll et al., 2003; Lease & Woodson, 2004; Afonyushkin et al., 2005). A similar mode of binding to sRNA was recently observed for the archaeal Lsm from *Haloferax volcanii* (Fischer et al., 2011).

As for the eukaryotic Lsm proteins, Hfq is required for deadenylation-dependent mRNA decay. An RNase E-Hfq-sRNA complex is thought to function in translational repression and subsequent mRNA destabilization and degradation (Morita et al., 2005; Morita et al., 2006). Additional functions of Hfq include ATPase activity (Sukhodolets & Garges, 2003), cellular stress response and modulation of virulence in some bacterial strains (Tsui et al., 1994; Fantappie et al., 2009; Liu et al., 2010). Interestingly, the virulence of the multi-drug resistant human pathogen *S. aureus* was decreased in Hfq-deletion strains. (Liu et al., 2010).

6. Lsm proteins in human disease and viral replication

Aberrations in functions of Lsm proteins have been associated with a number of human diseases. Sm proteins are known to be targeted by auto-antibodies in systemic lupus erythematosis (Lerner & Steitz, 1979). In fact, the proteins were first identified in nuclear extracts of a patient suffering from this disease. A mutation of the SMN gene resulting in diminished assembly of snRNPs is the cause of spinal muscular atrophy (Lefebvre et al., 1995; Wan et al., 2005). Three Lsm proteins (Lsm1, Lsm3 and Lsm7) have now been directly connected to different cancer types. Lsm1 (also named cancer associated Sm-like protein, CaSm) was upregulated in pancreatic, prostate and breast cancer, as well as in several cancer-derived cell lines (Schweinfest et al., 1997; Fraser et al., 2005; Streicher et al., 2007). Remarkably, overexpression of antisense Lsm1 has been demonstrated to promote tumor reduction (Kelley et al., 2000; Kelley et al., 2001; Yan et al., 2006). Elevated levels of Lsm7 have been identified in malignant thyroid tumors, and a reduction in Lsm7 expression was observed in breast cancers (Conte et al., 2002; Rosen et al., 2005). The copy number and expression for the Lsm3 gene was found to be elevated in cervical cancer (Lyng et al., 2006).

Observations concerning Lsm proteins in viral replication underlines some interesting functional diversity. Bacterial Hfq was initially described as a host factor required for phage Qß replication (Franze de Fernandez et al., 1968). A role for Lsm1 as an effector of HIV replication has been reported (Chable-Bessia et al., 2009). It has also been suggested more recently that positive-strand RNA viruses may directly bind to the host Lsm1-7 protein complex via tRNA-like structures and A-rich stretches, so diverting normal mRNA

regulation (Galao et al., 2010). The requirement of host Lsm proteins for the replication of this class of virus has additionally been demonstrated in plant brome mosaic virus (Diez et al., 2000; Noueiry et al., 2003; Mas et al., 2006) and human hepatitis C virus (Scheller et al., 2009).

7. References

Achsel, T., Brahms, H., Kastner, B., Bachi, A., Wilm, M., and Luerhmann, R. (1999), 'A doughnut-shaped heteromer of human Sm-like proteins binds to the 3' end of U6 snRNA, thereby facilitating U4/U6 duplex formation in vitro', *EMBO J,* 18 (20), 5789-802.

Afonyushkin, T., Vecerek, B., Moll, I., Blasi, U., and Kaberdin, V. R. (2005), 'Both RNase E and RNase III control the stability of sodB mRNA upon translational inhibition by the small regulatory RNA RyhB', *Nucleic Acids Res,* 33 (5), 1678-89.

Albrecht, M. and Lengauer, T. (2004), 'Novel Sm-like proteins with long C-terminal tails and associated methyltransferases', *FEBS Lett,* 569 (1-3), 18-26.

Anantharaman, V. and Aravind, L. (2004), 'Novel conserved domains in proteins with predicted roles in eukaryotic cell-cycle regulation, decapping and RNA stability', *BMC Genomics,* 5 (1), 45.

Balbo, P. B. and Bohm, A. (2007), 'Mechanism of poly(A) polymerase: structure of the enzyme-MgATP-RNA ternary complex and kinetic analysis', *Structure,* 15 (9), 1117-31.

Beggs, J. D. (2005), 'Lsm proteins and RNA processing', *Biochem Soc Trans* 33, 439-501.

Boeck, R., Lapeyre, B., Brown, C. E., and Sachs, A. B. (1998), 'Capped mRNA degradation intermediates accumulate in the yeast spb8-2 mutant', *Mol Cell Biol,* 18 (9), 5062-72.

Bonnerot, C., Boeck, R., and Lapeyre, B. (2000), 'The two proteins Pat1p (Mrt1p) and Spb8p interact in vivo, are required for mRNA decay, and are functionally linked to Pab1p.', *Mol Cell Biol,* 20.

Bouveret, E., Rigaut, G., Shevchenko, A., Wilm, M., and Seraphin, B. (2000), 'A Sm-like protein complex that participates in mRNA degradation', *EMBO J,* 19 (7), 1661-71.

Brengues, M., Teixeira, D., and Parker, R. (2005), 'Movement of eukaryotic mRNAs between polysomes and cytoplasmic processing bodies', *Science,* 310 (5747), 486-9.

Brennan, R. G. and Link, T. M. (2007), 'Hfq structure, function and ligand binding', *Curr Opin Microbiol,* 10 (2), 125-33.

Brow, D. A. (2002), 'Allosteric cascade of spliceosome activation', *Annu Rev Genet,* 36, 333-60.

Chable-Bessia, C., Meziane, O., Latreille, D., Triboulet, R., Zamborlini, A., Wagschal, A., Jacquet, J. M., Reynes, J., Levy, Y., Saib, A., Bennasser, Y., and Benkirane, M. (2009), 'Suppression of HIV-1 replication by microRNA effectors', *Retrovirology,* 6, 26.

Chowdhury, A., Mukhopadhyay, J. , and Tharun, S. (2007), 'The decapping activator Lsm1p-7p–Pat1p complex has the intrinsic ability to distinguish between oligoadenylated and polyadenylated RNAs', *RNA,* 13.

Coller, JM., Tucker, M., Sheth, U., Valencia-Sanchez, MA., and Parker, R. (2001), 'The DEAD box helicase, Dhh1p, functions in mRNA decapping and interacts with both the decapping and deadenylase complexes.', *RNA,* 7.

Collins, BM., Harrop, SJ., Kornfeld, GD., Ian, DW, Curmi, PMG., and Mabbutt, BC. (2001), 'Crystal Structure of a Heptameric Sm-like Protein Complex from Archea: Implications for the Structure and Evolution of snRNPs', *J Mol Biol,* 309, 915-23.

Conte, N., Charafe-Jauffret, E., Delaval, B., Adelaide, J., Ginestier, C., Geneix, J., Isnardon, D., Jacquemier, J., and Birnbaum, D. (2002), 'Carcinogenesis and translational controls: TACC1 is down-regulated in human cancers and associates with mRNA regulators', *Oncogene,* 21 (36), 5619-30.

Crick, F. (1979), 'Split genes and RNA splicing', *Science,* 204 (4390), 264-71.

Das, D., Kozbial, P., Axelrod, H. L., Miller, M. D., McMullan, D., Krishna, S. S., Abdubek, P., Acosta, C., Astakhova, T., Burra, P., Carlton, D., Chen, C., Chiu, H. J., Clayton, T., Deller, M. C., Duan, L., Elias, Y., Elsliger, M. A., Ernst, D., Farr, C., Feuerhelm, J., Grzechnik, A., Grzechnik, S. K., Hale, J., Han, G. W., Jaroszewski, L., Jin, K. K., Johnson, H. A., Klock, H. E., Knuth, M. W., Kumar, A., Marciano, D., Morse, A. T., Murphy, K. D., Nigoghossian, E., Nopakun, A., Okach, L., Oommachen, S., Paulsen, J., Puckett, C., Reyes, R., Rife, C. L., Sefcovic, N., Sudek, S., Tien, H., Trame, C., Trout, C. V., van den Bedem, H., Weekes, D., White, A., Xu, Q., Hodgson, K. O., Wooley, J., Deacon, A. M., Godzik, A., Lesley, S. A., and Wilson, I. A. (2009), 'Crystal structure of a novel Sm-like protein of putative cyanophage origin at 2.60 A resolution', *Proteins,* 75 (2), 296-307.

Diez, J., Ishikawa, M., Kaido, M., and Ahlquist, P. (2000), 'Identification and characterization of a host protein required for efficient template selection in viral RNA replication', *Proc Natl Acad Sci U S A,* 97 (8), 3913-8.

Eddy, S. R. (2001), 'Non-coding RNA genes and the modern RNA world', *Nat Rev Genet,* 2 (12), 919-29.

Fantappie, L., Metruccio, M. M., Seib, K. L., Oriente, F., Cartocci, E., Ferlicca, F., Giuliani, M. M., Scarlato, V., and Delany, I. (2009), 'The RNA chaperone Hfq is involved in stress response and virulence in Neisseria meningitidis and is a pleiotropic regulator of protein expression', *Infect Immun,* 77 (5), 1842-53.

Fernandez, C. F., Pannone, B. K., Chen, X., Fuchs, G., and Wolin, S. L. (2004), 'An Lsm2-Lsm7 complex in Saccharomyces cerevisiae associates with the small nucleolar RNA snR5', *Mol Biol Cell,* 15 (6), 2842-52.

Fischer, S., Benz, J., Spath, B., Maier, L. K., Straub, J., Granzow, M., Raabe, M., Urlaub, H., Hoffmann, J., Brutschy, B., Allers, T., Soppa, J., and Marchfelder, A. (2011), 'The archaeal Lsm protein binds to small RNAs', *J Biol Chem,* 285 (45), 34429-38.

Franze de Fernandez, M. T., Eoyang, L., and August, J. T. (1968), 'Factor fraction required for the synthesis of bacteriophage Qbeta-RNA', *Nature,* 219 (5154), 588-90.

Fraser, M. M., Watson, P. M., Fraig, M. M., Kelley, J. R., Nelson, P. S., Boylan, A. M., Cole, D. J., and Watson, D. K. (2005), 'CaSm-mediated cellular transformation is associated with altered gene expression and messenger RNA stability', *Cancer Res,* 65 (14), 6228-36.

Fromont-Racine, M., Rain, JC., and Legrain, P. (1997), 'Toward a functional analysis of the yeast genome through exhaustive two-hybrid screens.', *Nat Genetics,* 16.

Fromont-Racine, M., Mayes, A. E., Brunet-Simon, A., Rain, J. C., Colley, A., Dix, I., Decourty, L., Joly, N., Ricard, F., Beggs, J. D., and Legrain, P. (2000), 'Genome-wide protein interaction screens reveal functional networks involving Sm-like proteins', *Yeast,* 17 (2), 95-110.

Galao, R. P., Chari, A., Alves-Rodrigues, I., Lobao, D., Mas, A., Kambach, C., Fischer, U., and Diez, J. (2010), 'LSm1-7 complexes bind to specific sites in viral RNA genomes and regulate their translation and replication', *RNA,* 16 (4), 817-27.

Garneau, Nicole L., Wilusz, Jeffrey, and Wilusz, Carol J (2007), 'The highways and byways of mRNA decay', *Nat Rev Mol Cell Biol,* 8, 113-26.

Gottesman, S. and Storz, G. (2010), 'Bacterial Small RNA Regulators: Versatile Roles and Rapidly Evolving Variations', *Cold Spring Harb Perspect Biol*.

He, W. and Parker, R. (2001), 'The yeast cytoplasmic LsmI/Pat1p complex protects mRNA 3' termini from partial degradation', *Genetics,* 158 (4), 1445-55.

Kambach, Christian, Walke, Stefan, Young, Robert, Avis, Johanna M, de la Fortelle, Eric , Raker, Veronica A, Luerhmann, Reinhard, Li, Jade, and Nagai, Kiyoshi (1999), 'Crystal Structures of Two Sm Protein Complexes and Their Implications for the Assembly of the Spliceosomal snRNPs', *Cell,* 96, 375-87.

Karaduman, R., Fabrizio, P., Hartmuth, K., Urlaub, H., and Luerhmann, R. (2006), 'RNA structure and RNA-Protein interactions in Purified Yeast U6 snRNPs', *J Mol Biol,* 356, 1248-62.

Karaduman, R., Dube, P., Stark, H., Fabrizio, P., Kastner, B., and Luhrmann, R. (2008), 'Structure of yeast U6 snRNPs: arrangement of Prp24p and the LSm complex as revealed by electron microscopy', *RNA,* 14 (12), 2528-37.

Kelley, J. R., Fraser, M. M., Schweinfest, C. W., Vournakis, J. N., Watson, D. K., and Cole, D. J. (2001), 'CaSm/gemcitabine chemo-gene therapy leads to prolonged survival in a murine model of pancreatic cancer', *Surgery,* 130 (2), 280-8.

Kelley, J. R., Brown, J. M., Frasier, M. M., Baron, P. L., Schweinfest, C. W., Vournakis, J. N., Watson, D. K., and Cole, D. J. (2000), 'The cancer-associated Sm-like oncogene: a novel target for the gene therapy of pancreatic cancer', *Surgery,* 128 (2), 353-60.

Khusial, P., Plaag, R., and Zieve, GW. (2005), 'LSm proteins form heptameric rings that bind to RNA via repeating motifs', *Trends Biochem Sci* 30 (9).

Kufel, J., Bousquet-Antonelli, C., Beggs, J. D., and Tollervey, D. (2004), 'Nuclear pre-mRNA decapping and 5' degradation in yeast require the Lsm2-8p complex', *Mol Cell Biol,* 24 (21), 9646-57.

Kufel, J., Allmang, C., Verdone, L., Beggs, J. D., and Tollervey, D. (2002), 'Lsm proteins are required for normal processing of pre-tRNAs and their efficient association with La-homologous protein Lhp1p', *Mol Cell Biol,* 22 (14), 5248-56.

Kufel, J., Allmang, C., Verdone, L., Beggs, J., and Tollervey, D. (2003a), 'A complex pathway for 3' processing of the yeast U3 snoRNA', *Nucleic Acids Res,* 31 (23), 6788-97.

Kufel, J., Allmang, C., Petfalski, E., Beggs, J., and Tollervey, D. (2003b), 'Lsm Proteins are required for normal processing and stability of ribosomal RNAs', *J Biol Chem,* 278 (4), 2147-56.

Lease, R. A. and Woodson, S. A. (2004), 'Cycling of the Sm-like protein Hfq on the DsrA small regulatory RNA', *J Mol Biol,* 344 (5), 1211-23.

Lefebvre, S., Burglen, L., Reboullet, S., Clermont, O., Burlet, P., Viollet, L., Benichou, B., Cruaud, C., Millasseau, P., Zeviani, M., and et al. (1995), 'Identification and characterization of a spinal muscular atrophy-determining gene', *Cell,* 80 (1), 155-65.

Lerner, M. R. and Steitz, J. A. (1979), 'Antibodies to small nuclear RNAs complexed with proteins are produced by patients with systemic lupus erythematosus', *Proc Natl Acad Sci U S A,* 76 (11), 5495-9.

Li, Z., Lee, I., Moradi, E., Hung, N. J., Johnson, A. W., and Marcotte, E. M. (2009), 'Rational extension of the ribosome biogenesis pathway using network-guided genetics', *PLoS Biol,* 7 (10), e1000213.

Licht, K., Medenbach, J., Luerhmann, R., Kambach, C., and Bindereif, A. (2008), '3'-cyclic phosphorylation of U6 snRNA leads to recruitment of recycling factor p110 through LSm proteins', *RNA,* 14 (8), 1-7.

Lilley, D. M. (2005), 'Structure, folding and mechanisms of ribozymes', *Curr Opin Struct Biol,* 15 (3), 313-23.

Ling, S. H., Decker, C. J., Walsh, M. A., She, M., Parker, R., and Song, H. (2008), 'Crystal structure of human Edc3 and its functional implications', *Mol Cell Biol,* 28 (19), 5965-76.

Link, T. M., Valentin-Hansen, P., and Brennan, R. G. (2009), 'Structure of Escherichia coli Hfq bound to polyriboadenylate RNA', *Proc Natl Acad Sci U S A,* 106 (46), 19292-7.

Liu, Y., Wu, N., Dong, J., Gao, Y., Zhang, X., Mu, C., Shao, N., and Yang, G. (2010), 'Hfq is a global regulator that controls the pathogenicity of Staphylococcus aureus', *PLoS One,* 5 (9):e13069.

Livny, J. and Waldor, M. K. (2007), 'Identification of small RNAs in diverse bacterial species', *Curr Opin Microbiol,* 10 (2), 96-101.

Luhrmann, R., Kastner, B., and Bach, M. (1990), 'Structure of spliceosomal snRNPs and their role in pre-mRNA splicing', *Biochim Biophys Acta,* 1087 (3), 265-92.

Lyng, H., Brovig, R. S., Svendsrud, D. H., Holm, R., Kaalhus, O., Knutstad, K., Oksefjell, H., Sundfor, K., Kristensen, G. B., and Stokke, T. (2006), 'Gene expressions and copy numbers associated with metastatic phenotypes of uterine cervical cancer', *BMC Genomics,* 7, 268.

Ma, Y., Dostie, J., Dreyfuss, G., and Van Duyne, G. D. (2005), 'The Gemin6-Gemin7 heterodimer from the survival of motor neurons complex has an Sm protein-like structure', *Structure,* 13 (6), 883-92.

Majdalani, N., Vanderpool, C. K., and Gottesman, S. (2005), 'Bacterial small RNA regulators', *Crit Rev Biochem Mol Biol,* 40 (2), 93-113.

Mas, A., Alves-Rodrigues, I., Noueiry, A., Ahlquist, P., and Diez, J. (2006), 'Host deadenylation-dependent mRNA decapping factors are required for a key step in brome mosaic virus RNA replication', *J Virol,* 80 (1), 246-51.

Mattick, J. S. (2001), 'Non-coding RNAs: the architects of eukaryotic complexity', *EMBO Rep,* 2 (11), 986-91.

Mattick, J. S. and Makunin, I. V. (2006), 'Non-coding RNA', *Hum Mol Genet,* 15 Spec No 1, R17-29.

Mayes, AE., Verdone, L., Legraine, P., and Beggs, JD. (1999), 'Characerization of Sm-like proteins in yeast and their association with U6 snRNA ', *EMBO J,* 18 (15), 4321-31.

Moll, I., Leitsch, D., Steinhauser, T., and Blasi, U. (2003), 'RNA chaperone activity of the Sm-like Hfq protein', *EMBO Rep,* 4 (3), 284-9.

Morita, T., Maki, K., and Aiba, H. (2005), 'RNase E-based ribonucleoprotein complexes: mechanical basis of mRNA destabilization mediated by bacterial noncoding RNAs', *Genes Dev,* 19 (18), 2176-86.

Morita, T., Mochizuki, Y., and Aiba, H. (2006), 'Translational repression is sufficient for gene silencing by bacterial small noncoding RNAs in the absence of mRNA destruction', *Proc Natl Acad Sci U S A,* 103 (13), 4858-63.

Mura, C., Phillips, M., Kozhukhovsky, A., and Eisenberg, D. (2003), 'Structure and assembly of an augmented Sm-like archaeal protein 14-mer', *Proc Natl Acad Sci U S A,* 100 (8), 4539-44.

Naidoo, N., Harrop, SJ., Sobti, M., Haynes, PA., Szymczyna, BR., Williamson, JR., Curmi, PMG., and Mabbutt, BC. (2008), 'Crystal Structure of Lsm3 Octamer from Saccharomyces cerevisiae: Implications for Lsm Ring Organisation and Recruitment', *J Mol Biol,* 377, 1357-71.

Nissan, T., Rajyaguru, P., She, M., Song, H., and Parker, R. (2010), 'Decapping activators in Saccharomyces cerevisiae act by multiple mechanisms', *Mol Cell,* 39 (5), 773-83.

Noueiry, A. O., Diez, J., Falk, S. P., Chen, J., and Ahlquist, P. (2003), 'Yeast Lsm1p-7p/Pat1p deadenylation-dependent mRNA-decapping factors are required for brome mosaic virus genomic RNA translation', *Mol Cell Biol,* 23 (12), 4094-106.

Parker, R. and Sheth, U. (2007), 'P Bodies and the control of mRNA Translation and Degradation', *Mol Cell,* 25 (5), 635-46.

Patel, S. B. and Bellini, M. (2008), 'The assembly of a spliceosomal small nuclear ribonucleoprotein particle', *Nucleic Acids Res,* 36 (20), 6482-93.

Peng, R. and Gallwitz, D. (2004), 'Multiple SNARE interactions of an SM protein: Sed5p/Sly1p binding is dispensable for transport', *EMBO J,* 23 (20), 3939-49.

Pomeranz Krummel, D. A., Oubridge, C., Leung, A. K., Li, J., and Nagai, K. (2009), 'Crystal structure of human spliceosomal U1 snRNP at 5.5 A resolution', *Nature,* 458 (7237), 475-80.

Pozzoli, U., Sironi, M., Cagliani, R., Comi, G. P., Bardoni, A., and Bresolin, N. (2002), 'Comparative analysis of the human dystrophin and utrophin gene structures', *Genetics,* 160 (2), 793-8.

Proudfoot, N. J., Furger, A., and Dye, M. J. (2002), 'Integrating mRNA processing with transcription', *Cell,* 108 (4), 501-12.

Rader, S. D. and Guthrie, C. (2002), 'A conserved Lsm-interaction motif in Prp24 required for efficient U4/U6 di-snRNP formation', *RNA,* 8 (11), 1378-92.

Raker, VA., Hartmuth, K., Kastner, B., and Luhrmann, R. (1999), 'Spliceosomal U snRNP core assembly: Sm proteins assemble onto an Sm site RNA nonanucleotide in a specific and thermodynamically stable manner', *Mol Cell Biol,* 19 (10), 6554-65.

Reijns, M. A., Auchynnikava, T., and Beggs, J. D. (2009), 'Analysis of Lsm1p and Lsm8p domains in the cellular localization of Lsm complexes in budding yeast', *FEBS J,* 276 (13), 3602-17.

Reijns, M. A., Alexander, R. D., Spiller, M. P., and Beggs, J. D. (2008), 'A role for Q/N-rich aggregation-prone regions in P-body localization', *J Cell Sci,* 121 (Pt 15), 2463-72.

Rosen, J., He, M., Umbricht, C., Alexander, H. R., Dackiw, A. P., Zeiger, M. A., and Libutti, S. K. (2005), 'A six-gene model for differentiating benign from malignant thyroid tumors on the basis of gene expression', *Surgery,* 138 (6), 1050-6; discussion 56-7.

Ryan, D. E., Stevens, S. W., and Abelson, J. (2002), 'The 5' and 3' domains of yeast U6 snRNA: Lsm proteins facilitate binding of Prp24 protein to the U6 telestem region', *RNA,* 8 (8), 1011-33.

Salgado-Garrido, J., Bragado-Nielsson, E., Kandels-Lewis, S., and Seraphin, B. (1999), 'Sm and Sm-like proteins assemble in two related complexes of deep evolutionary origin', *EMBO J,* 18 (12), 3451-62.

Scheller, N., Mina, L. B., Galao, R. P., Chari, A., Gimenez-Barcons, M., Noueiry, A., Fischer, U., Meyerhans, A., and Diez, J. (2009), 'Translation and replication of hepatitis C virus genomic RNA depends on ancient cellular proteins that control mRNA fates', *Proc Natl Acad Sci U S A,* 106 (32), 13517-22.

Schumacher, MA., Pearson, RF., Moller, T., Valentin-Hansen, P., and Brennan, RG. (2002), 'Structures of the pleiotropic translational regulator Hfq and an Hfq-RNA complex: a bacterial Sm-like protein', *EMBO J,* 21 (13), 3546-56.

Schweinfest, C. W., Graber, M. W., Chapman, J. M., Papas, T. S., Baron, P. L., and Watson, D. K. (1997), 'CaSm: an Sm-like protein that contributes to the transformed state in cancer cells', *Cancer Res,* 57 (14), 2961-5.

Selenko, P., Sprangers, R., Stier, G., Buhler, D., Fischer, U., and Sattler, M. (2001), 'SMN tudor domain structure and its interaction with the Sm proteins', *Nat Struct Biol,* 8 (1), 27-31.

Sheth, U. and Parker, R. (2003), 'Decapping and decay of messenger RNA occur in cytoplasmic processing bodies', *Science,* 300 (5620), 805-8.

Sobti, M., Cubeddu, L., Haynes, P. A., and Mabbutt, B. C. (2010), 'Engineered rings of mixed yeast Lsm proteins show differential interactions with translation factors and U-rich RNA', *Biochemistry,* 49 (11), 2335-45.

Song, M. G. and Kiledjian, M. (2007), '3' Terminal oligo U-tract-mediated stimulation of decapping', *RNA,* 13 (12), 2356-65.

Spiller, M. P., Boon, K. L., Reijns, M. A., and Beggs, J. D. (2007), 'The Lsm2-8 complex determines nuclear localization of the spliceosomal U6 snRNA', *Nucleic Acids Res,* 35 (3), 923-9.

Storz, G., Opdyke, J. A., and Zhang, A. (2004), 'Controlling mRNA stability and translation with small, noncoding RNAs', *Curr Opin Microbiol,* 7 (2), 140-4.

Streicher, K. L., Yang, Z. Q., Draghici, S., and Ethier, S. P. (2007), 'Transforming function of the LSM1 oncogene in human breast cancers with the 8p11-12 amplicon', *Oncogene,* 26 (14), 2104-14.

Sukhodolets, M. V. and Garges, S. (2003), 'Interaction of Escherichia coli RNA polymerase with the ribosomal protein S1 and the Sm-like ATPase Hfq', *Biochemistry,* 42 (26), 8022-34.

Tharun, S., He, W., Mayes, A. E., Lennertz, P., Beggs, J. D., and Parker, R. (2000), 'Yeast Sm-like proteins function in mRNA decapping and decay', *Nature,* 404 (6777), 515-8.

Thore, S., Mayer, C., Sauter, C., Weeks, S., and Suck, D. (2003), 'Crystal structures of the Pyrococcus abyssi Sm core and its complex with RNA. Common features of RNA binding in archaea and eukarya', *J Biol Chem,* 278 (2), 1239-47.

Tomasevic, N. and Peculis, B. A. (2002), 'Xenopus LSm proteins bind U8 snoRNA via an internal evolutionarily conserved octamer sequence', *Mol Cell Biol,* 22 (12), 4101-12.

Toro, I., Basquin, J., Teo-Dreher, H., and Suck, D. (2002), 'Archaeal Sm proteins form heptameric and hexameric complexes: crystal structures of the Sm1 and Sm2 proteins from the hyperthermophile Archaeoglobus fulgidus', *J Mol Biol,* 320 (1), 129-42.

Toro, I., Thore, Stephane , Mayer, Claudine, Basquin, Jerome, Seraphin, Bertrand, and Suck, Dietrich (2001), 'RNA binding in an Sm core domain: X-ray structure and functional analysis of an archeal Sm protein complex', *EMBO J,* 20 (9), 2293-303.

Tritschler, F., Eulalio, A., Truffault, V., Hartmann, M. D., Helms, S., Schmidt, S., Coles, M., Izaurralde, E., and Weichenrieder, O. (2007), 'A divergent Sm fold in EDC3 proteins mediates DCP1 binding and P-body targeting', *Mol Cell Biol,* 27 (24), 8600-11.

Tsui, H. C., Leung, H. C., and Winkler, M. E. (1994), 'Characterization of broadly pleiotropic phenotypes caused by an hfq insertion mutation in Escherichia coli K-12', *Mol Microbiol,* 13 (1), 35-49.

Tucker, M., Valencia-Sanchez, M. A., Staples, R. R., Chen, J., Denis, C. L., and Parker, R. (2001), 'The transcription factor associated Ccr4 and Caf1 proteins are components of the major cytoplasmic mRNA deadenylase in Saccharomyces cerevisiae', *Cell,* 104 (3), 377-86.

Urlaub, H., Raker, V. A., Kostka, S., and Luhrmann, R. (2001), 'Sm protein-Sm site RNA interactions within the inner ring of the spliceosomal snRNP core structure', *EMBO J,* 20 (1-2), 187-96.

Verdone, L., Galardi, S., Page, D., and Beggs, J. D. (2004), 'Lsm proteins promote regeneration of pre-mRNA splicing activity', *Curr Biol,* 14 (16), 1487-91.

Veretnik, S., Wills, C., Youkharibache, P., Valas, R. E., and Bourne, P. E. (2009), 'Sm/Lsm genes provide a glimpse into the early evolution of the spliceosome', *PLoS Comput Biol,* 5 (3), e1000315.

Wahl, M. C., Will, C. L., and Luhrmann, R. (2009), 'The spliceosome: design principles of a dynamic RNP machine', *Cell,* 136 (4), 701-18.

Wan, L., Battle, D. J., Yong, J., Gubitz, A. K., Kolb, S. J., Wang, J., and Dreyfuss, G. (2005), 'The survival of motor neurons protein determines the capacity for snRNP assembly: biochemical deficiency in spinal muscular atrophy', *Mol Cell Biol,* 25 (13), 5543-51.

Wassarman, K. M., Repoila, F., Rosenow, C., Storz, G., and Gottesman, S. (2001), 'Identification of novel small RNAs using comparative genomics and microarrays', *Genes Dev,* 15 (13), 1637-51.

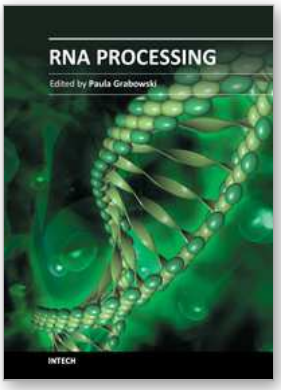
Weber, G., Trowitzsch, S., Kastner, B., Luhrmann, R., and Wahl, M. C. (2010), 'Functional organization of the Sm core in the crystal structure of human U1 snRNP', *EMBO J,* 29 (24), 4172-84.

Wen, Y. and Shatkin, A. J. (1999), 'Transcription elongation factor hSPT5 stimulates mRNA capping', *Genes Dev,* 13 (14), 1774-9.

Will, C. L. and Luhrmann, R. (2001), 'Spliceosomal UsnRNP biogenesis, structure and function', *Curr Opin Cell Biol,* 13 (3), 290-301.

Wolin, S. L. and Cedervall, T. (2002), 'The La protein', *Annu Rev Biochem,* 71, 375-403.

Yan, Y., Rubinchik, S., Wood, A. L., Gillanders, W. E., Dong, J. Y., Watson, D. K., and Cole, D. J. (2006), 'Bystander effect contributes to the antitumor efficacy of CaSm antisense gene therapy in a preclinical model of advanced pancreatic cancer', *Mol Ther,* 13 (2), 357-65.



RNA Processing

Edited by Prof. Paula Grabowski

ISBN 978-953-307-557-0
Hard cover, 248 pages
Publisher InTech
Published online 29, August, 2011
Published in print edition August, 2011

RNA functions broadly as informational molecule, genome, enzyme and machinery for RNA processing. While these functions reflect ancient activities, they also remain vital components of contemporary biochemical pathways. In eukaryotic cells RNA processing impacts the biogenesis of RNA molecules of essentially every shape and function. The collection of articles in this volume describes the current state of understanding of the broad array of RNA processing events in animal and plant cells, key unanswered questions, and cutting edge approaches available to address these questions. Some questions discussed in this volume include, how viruses subvert the RNA processing machinery of the host cell, how the coordination of co-transcriptional RNA processing is regulated at the level of chromatin, the status of RNA processing in plant organelles, and how micro RNA machinery is biosynthesized and regulated.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821