Editorial

Structural basis for assembly and function of the 7SK snRNP complex

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RNA plays a central role in the precise control of several biological processes including transcription, translation and DNA replication. As such, correct function of RNA-mediated processes is vital for maintaining cell homeostasis thereby avoiding malignancy. The recent structure of human LARP7 and its binding site on 7SK RNA by Feigon and co-workers (1) reveals molecular details into how this protein-RNA interaction contributes to 7SK RNA recognition and provides insights into the assembly of the 7SK small nuclear ribonucleoprotein (snRNP) complex for correct transcriptional control.

The 7SK snRNP complex is composed of 7SK RNA (331-nt) (*Figure 1A*) and four core protein components: the positive transcription elongation factor (P-TEFb) kinase, the kinase inhibitor hexamethylene bis-acetamide-inducible protein 1/2 (here referred to as HEXIM), the La-related protein 7 (LARP7), and the Methylphosphate capping enzyme (MePCE) (*Figure 1B*) [reviewed in (2-4)]. P-TEFb, which is composed of cyclin-dependent kinase 9 (CDK9) and its activator CyclinT1/2 (CycT) (*Figure 1B*), is one of the major RNA polymerase II (Pol II) kinases that phosphorylates Ser2 residues in the $Y_1S_2P_3T_4S_5P_6S_7$ heptad repeats of the Pol II C-terminal domain to promote transcriptional pause release and increase Pol II processivity [reviewed in (3)].

Breakthrough work by the Zhou and Bensaude labs in 2001 have defined a key role for 7SK RNA, one of the most abundant non-coding RNAs in the cell (5), in the control of P-TEFb-mediated Pol II transcription (6,7). In these pioneer studies, 7SK RNA was shown to play a pivotal role in the reversible inactivation of P-TEFb kinase activity toward its substrates (Pol II and negative elongation factors) thereby restricting transcription elongation (3). Regulation of kinase activity was then attributed to the HEXIM kinase inhibitor through cooperative recruitment of P-TEFb to the 7SK RNA (8-11). These studies collectively provided a basic understanding of the mechanism of kinase inhibition and Pol II transcriptional control for the precise regulation of cell growth and differentiation with a non-coding RNA.

A diverse set of approaches including chemical probing, modeling and structure determination (5,12,13) have revealed that 7SK RNA primarily folds into four stem loops (SL) (*Figure 1A*) that provide scaffolds for binding its protein partners (*Figure 1B*). The apical region of SL1 (G24-C48 and C60-G87) contains a conserved, repeated GAUC motif flanked by U-rich bulges, which contacts one Arginine Rich Motif (ARM, amino acids 152-155 (*Figure 1C*)) in the central domain of a HEXIM homo-dimer (9,11,14,15) (*Figure 1A,B*). ARM binding promotes local conformational rearrangements in SL1 through opening of the GAUC motif and stabilization of an internal loop for assembling the homo-dimer, providing evidence of 7SK RNA plasticity in the control of Pol II transcription (14).

HEXIM has been characterized as a promiscuous RNA binding protein with low structural complexity in its ARM. Thus, the structural dynamics of the GAUC motif—ARM binding might provide the molecular basis for how HEXIM specifically singles out 7SK RNA within the pool

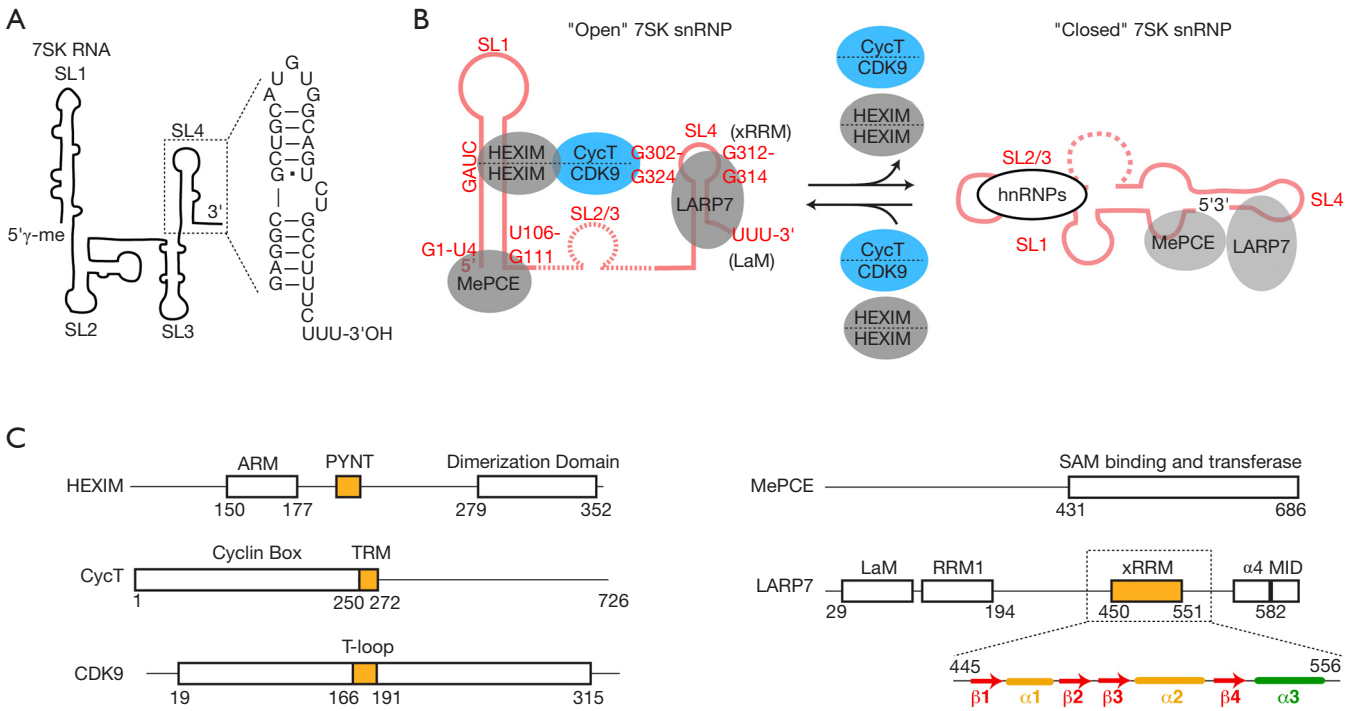

Figure 1 7SK snRNP complex components and their interactions. (A) Scheme of 7SK RNA and its stem loops (SL). The sequence of SL4 used for the structural work is indicated. γ-me, denotes the presence of the γ-methylphosphate cap in the 5'-end (SL1); (B) scheme of the protein-protein and protein-RNA interactions that facilitate assembly of the 7SK snRNP. HEXIM binds the GAUC motif and MePCE binds the G1–U4/U106–G111 residues in SL1 of 7SK RNA, while LARP7 and P-TEFb (composed of the CDK9/CycT complex) contact SL4. This constitutes the open form of the 7SK RNP. In the closed form, the LARP7 MID module binds and inhibits MePCE thereby promoting interactions between SL1 and SL4; (C) domain structure of the protein components of the 7SK snRNP. HEXIM's ARM contacts SL1 while the PYNT domain binds and directly inhibits CDK9. The cyclin box domain of CycT interacts with CDK9 while the CycT1 TRM binds SL4. Phosphorylation of the T-loop of CDK9 (not shown for simplicity) is essential for 7SK snRNP assembly (2). The C-terminal region of MePCE is known to be involved in SAM binding and methyl-transferase activity. LARP7 protein has genuine La module and two RNA binding motifs (RRM1 and xRRM). The xRRM domain used for the structural work by Feigon and co-workers and its βαββαβ topology are highlighted.

of other non-specific RNAs in the nucleus. In addition to HEXIM's ARM, its C-terminal domain [amino acids 181-359 (*Figure 1C*)] directly contacts P-TEFb for direct kinase inactivation (11). The C-terminal domain contains the coiled-coil dimerization region (16) that binds the CycT subunit of P-TEFb and the evolutionarily conserved PYNT motif [amino acids 202-205 (*Figure 1C*)] that binds the catalytic cleft of CDK9 to inhibit kinase function in the 7SK snRNP complex (17). These data together provided a molecular understanding for the division of labors in HEXIM modular organization, as well as an ordered recruitment mechanism in which HEXIM first binds the apical loop of 7SK RNA SL1, which is a prerequisite for association of P-TEFb with the apical region of 7SK RNA SL4 (G302-C324) (*Figure 1B*) for kinase inactivation (11).

Besides 7SK RNA, P-TEFb and HEXIM, the 7SK snRNP complex contains two additional subunits: LARP7 and MePCE (*Figure 1B*), which stably associate with 7SK RNA and have more than structural scaffolding functions [reviewed in (2-4)]. LARP7 belongs to a large family of La and LARPs (18,19). Four families of LARPs emerged during eukaryotic evolution with specialized functions. Amongst all four LARP families, LARP7 family members most closely resemble La but function with a single Pol III transcript (7SK, U6 or telomerase RNA), unlike other La's that are typically more promiscuous and bind multiple RNA targets, to regulate unique RNA-based processes (19).

It has been known for some time that LARP7 is required

for 7SK RNA stability and for hierarchical assembly of the 7SK snRNP complex with key implications for control of epithelial cell differentiation and to prevent P-TEFb-dependent malignant transformation (20-22). LARP7 binds two regions of 7SK RNA SL4 using distinct protein surfaces (*Figure 1B*). First, the N-terminal La domain (*Figure 1C*) binds and protects the 3'-UUU-OH tail from degradation. Second, an atypical RNA recognition motif termed xRRM (*Figure 1C*), first identified in the *Tetrahymena thermophile* telomerase LARP7 protein p65 (23), binds to the apical portion of SL4 interacting with both unpaired (residues G312 to G314 in the apical loop) and base-paired nucleotides (major groove of the SL4 helix) (21,24,25) (*Figure 1B,C*), exemplifying the evolutionary conserved role of the xRRM domain in non-coding RNA recognition. Importantly, besides providing stability for 7SK, LARP7 (likewise HEXIM) participates in P-TEFb regulation by directly controlling its incorporation into the 7SK snRNP complex through interaction with CDK9 (*Figure 1B*) (26,27). This data thus provided a molecular understanding for LARP7 RNA-binding somatic mutations in cancer development through uncontrolled P-TEFb function and target oncogene activation (22,27).

The MePCE protein, first discovered by the Coulombe lab, contains the methyltransferase domain with a typical 'Rossman' fold and uses S-adenosyl methionine (SAM) (*Figure 1C*) to transfer a methyl group to the γ-phosphate of the 5'-G of 7SK RNA (*Figure 1A*). This cap protects 7SK RNA from degradation by cellular factors thus promoting 7SK snRNP complex stability (28,29). MePCE binds both the 5'-end of 7SK RNA (SL1) interacting with G1-U4/U106-G111 helix-tail motif and LARP7 to facilitate assembly of the core 7SK RNP sub-complex composed of 7SK/MePCE/LARP7 (27). This core sub-complex remains intact without P-TEFb and HEXIM under stress conditions (heat shock and DNA damage) and assembles first to recruit P-TEFb (30). This process is further exemplified by mutations in 7SK RNA SL4 that disrupt LARP7 binding and abolish P-TEFb recruitment by 7SK RNA without affecting the organization of the core 7SK RNP sub-complex (27).

7SK RNA is highly dynamic and exhibits local and global conformational changes dependent on its interacting partners (*Figure 1B*) (13). For instance, both 7SK RNA SL1 and SL4 contain multiple Arginine Sandwich Motifs (ASM), which are poised for interacting with the RNA-binding domains of HEXIM and LARP7. The 5'-end of 7SK RNA pairs alternatively with two different regions giving rise to open and closed conformations (*Figure 1B*), which could be caused by interactions with different factors (13), such as HEXIM and P-TEFb in the open conformation, and heterogeneous nuclear ribonucleoproteins (hnRNPs) in the closed core RNP conformation (13,31). In the canonical open conformation that sequesters P-TEFb, 7SK RNA is capped by the LARP7-free MePCE protein (30). In the closed conformation, the C-terminal MePCE interaction motif (MID) of LARP7 (*Figure 1C*) binds MePCE and inhibits its capping activity thus mediating interactions between 7SK RNA SL1 and SL4 (*Figure 1B*) (13). These conformational changes thus provide insights into how the intra-molecular interactions within the 7SK snRNP complex directly impact the functions of its subunits (13,24).

Despite this progress on the molecular mechanism of 7SK snRNP complex assembly and function, the structure of 7SK snRNP protein components with the RNA has remained elusive. Individual 7SK RNA SL structures and few of its bipartite interactions with protein binders have been determined using NMR spectroscopy and X-ray crystallography (15,24,32-34). For instance, the solution structure of the 5'-end of 7SK RNA (SL1) as well as the free and Arg-bound forms of 3'-end of 7SK RNA (SL4) have been known for some time (32,34), but no structural details about the LARP7-7SK protein-RNA interactions or its relationship to the 7SK snRNP complex had been revealed. That is, until the recent high-resolution (2.2Å) crystal structure of the LARP7 xRRM bound to 7SK RNA SL4 from Feigon and co-workers (1). This breakthrough study, which relied on purification of the LARP7 xRRM domain, assembly with the RNA, and large-scale complex purification, provides deep insights into the assembly of the 7SK snRNP complex. The structure also helps explain how LARP7 uses a pre-formed pocket to contact 7SK RNA to facilitate 7SK snRNP assembly and how interlacing xRRM-RNA contacts define the binding interface (*Figure 2A,B*). This study follows on the heels of a previous 7SK RNA structural analysis, which showed plasticity of the 7SK snRNP complex and the importance of protein-RNA and protein-protein contacts to mediate changes in RNA conformation during assembly/disassembly of P-TEFb–HEXIM into/from the complex (*Figure 1B*) (13).

LARP7 is composed of four discrete domains including the evolutionary conserved xRRM that contacts 7SK RNA SL4 (*Figure 1C*). In the crystal structure reported by Eichhorn *et al.*, the xRRM domain has the expected βαββαβ topology, consistent with the solution structure of free LARP7 xRRM (25). In addition, the last α-helix (α3) shows

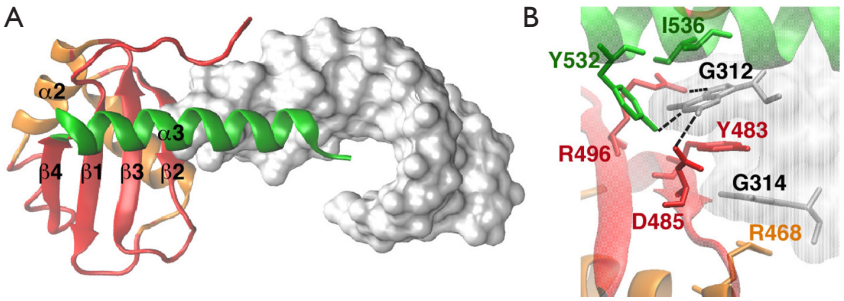

Figure 2 Structural details of the xRRM-SL4 assembly. (A) Side view of the LARP7 xRRM-7SK RNA SL4 complex (PDB 6D12). xRRM is denoted by ribbons representation following the same βαββαβ topology color scheme as in *Figure 1C*. SL4 is denoted by a solid grey surface mesh; (B) key residue level, side chain interactions within LARP7 xRRM-7SK RNA SL4 complex. G312 and G314 in the SL4 apical loop form a continuous π-π stacking interaction with Arg468, Tyr483 and Ile536 in the xRRM while Asp485, Tyr532 and Arg496 form hydrogen bonds (black dashed lines) with the Watson-Crick and Hoogstein faces of G312 respectively.

extensive interactions with 7SK RNA SL4 at the C-terminal contacting three key residues (A310, U311, and G312) and inserting into the RNA major groove (*Figure 2A*) forming an extensive interface over a buried surface area equal to 1312Å^2. A key feature of the binding interface is a five-residue (Arg468, Tyr483, Ile536, Gly312 and Gly314) stacking interaction (*Figure 2B*) composed of alternating protein residues in α1, β3 and α3 in the xRRM and flipped out RNA residues in the apical loop of SL4, consistent with previous NMR chemical shift mapping experiments (25). The highly conserved amino acids Tyr483 (β3 strand) and Arg496 (β3 strand) as well as 7SK RNA SL4 residue G312 (*Figure 2B*) build the core of the xRRM-RNA binding interface and significantly contribute to 7SK snRNP complex formation through stacking and hydrogen bond interactions, respectively.

One of the most striking features of the xRRM is a pre-organized pocket to bind loop 4 in the RNA, which differs from other well-known examples of induced fit in RNA-protein recognition (35). However, some reorganization is observed upon RNA binding. In the absence of 7SK RNA, the C-terminal of α3 (amino acids 541–544) is increasingly disordered (1), but upon RNA binding it is stabilized and reoriented ~14°, thus coming closer to the β sheet surface and showing additional electron density (amino acids 544–548). Some of the largest differences between the RNA free and bound forms occur at the N-terminus. While amino acids 446–454 are flexible in the free form, they become structured upon RNA binding indicating increased density due to stable protein-RNA contacts. However, despite this residue level insight, one caveat to comparing RNA-bound and unbound xRRM is that LARP7 in the bound structure contained two mutations (Glu501Leu and Gln504Leu) in helix α2 to reduce surface entropy and promote crystallization.

The 7SK RNA SL4, on the other hand, is flexible and experiences large conformational changes upon binding the xRRM. The apical loop residues (U311–G314) have low S2 order parameters in solution (calculated from ^{13}C spin relaxation NMR data) indicating that they are flexible in the free form and may assist in LARP7 binding through a conformational selection mechanism (1). For instance, G312 and G314 are in a syn conformation in the free form NMR solution structure (34) and loop out into anti conformation to make extensive contacts with the xRRM in the bound form crystal structure (1). Concurrently, the phosphodiester backbone between these residues also makes an S turn centered on U313 and further stabilizes the xRRM-SL4 interaction through an extended network of hydrogen bonds. Similarly, the upper part of SL4 stem has a widened major groove in the xRRM bound form, most likely due to the insertion of the α3 helix, and provides a large binding interface for the xRRM (*Figure 2A,B*).

To further understand the relationship of the LARP7-7SK protein-RNA interaction with the 7SK snRNP complex, Feigon and co-workers modeled the assembly of the core 7SK RNP sub-complex composed of 7SK/MePCE/LARP7 (27) using the available structures of SL4 nucleotides (34), xRRM bound to SL4 (1), RRM1/La module bound to 7SK 3'-UUU (24), the C-terminal domain of MePCE (PDB ID 5UNA) along with the predicted helical structure of LARP7 MID. In the modeled assembly, xRRM and the apical loop of SL4 form a stable complex consistent with the 2.2Å crystal structure (1);

however the 3'-UUU, La module and MID sample multiple conformations. In one of these positions, the RRM1 β2-β3 loop is open to interact with other RNAs, possibly 7SK 5'-end (24), and primes the MID to form an RNA-LARP7 dependent MePCE binding interface (1). Such conformational changes may bring LARP7 and MePCE in close proximity to assemble the core 7SK/MePCE/LARP7 sub-complex. However, in the absence of any high-resolution structural details of MID, LARP7 and MePCE protein-protein and protein-RNA interactions, it still remains highly challenging to decipher the mechanism by which these interactions promote the assembly of 7SK snRNP or its transition between the open and closed conformations (*Figure 1B*).

The structure from Feigon and co-workers (1) reveals structural details about the LARP7-7SK protein-RNA interaction and its relationship to the 7SK snRNP complex. However, like in every breakthrough story, several questions remain to our full understanding on the assembly, organization, and function of the 7SK snRNP complex. Some of these questions will be addressed by additional structural studies, most immediately of full LARP7 and 7SK RNA SL4 and the core 7SK/MePCE/LARP7 RNP sub-complex. While some information exists about how LARP7 and MePCE interact with each other and with the 7SK RNA, the structural basis for 7SK RNA recognition by both factors remains incomplete. It is possible that the interactions observed in the present structure will differ in the context of other factors present in the larger assembly. Some of these changes or conformational transitions may be important for the assembly, regulation, and function of the complex subunits, especially of the P-TEFb kinase. How LARP7 promotes P-TEFb interaction with 7SK RNA SL4 and 7SK snRNP assembly with HEXIM remains to be explored. However, structural studies of the full RNP complex have proven particularly challenging due to high instability and conformational flexibility of its components. For instance, 7SK snRNP reconstituted *in vitro* from heterologous, recombinant protein expression in eukaryotic systems has not yet yielded stable or homogeneous particles suitable for determination of a comprehensive structure by either X-ray crystallography or cryo-Electron Microscopy (EM). However, novel discoveries are still emerging that suggest that a structure of the full 7SK snRNP complex would be possible. The recent biochemical purification of a full, active 7SK snRNP from mammalian cells (13) is indicative that a path for a cryo-EM structure is feasible, pending determination of sample heterogeneity.

Importantly, the article by Feigon and co-workers clearly exemplify the need of using multiple structural biology approaches, such as NMR spectroscopy and X-ray crystallography, for more accurate and biologically informative structure determinations (36). Remarkably, the minimalistic LARP7-7SK RNA structure provides a starting point for deeper studies of the molecular mechanisms of 7SK snRNP complex assembly, P-TEFb kinase inactivation and the control of Pol II transcription elongation. Once again, structural biology provides a window into the function of RNA in key biological processes.

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Footnote

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