Oral Contributions

[MS6-02] Crystal structure of Prp8 and its implications for the spliceosomal active site.

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The Spliceosome is a dynamic molecular machine, which catalyzes excision of non-coding sequences (introns) from precursors of messenger RNAs (pre-mRNAs). It is assembled from 4 canonical subunits – small nuclear ribonucleoprotein particles (U1, U2, U4/U6 and U5 snRNPs) and number of other, non-snRNP factors. Each round of splicing requires hierarchical de novo assembly of spliceosomal subunits on pre-mRNA, followed by series of conformational and compositional rearrangements to form catalytically competent particle. The catalytic core of the spliceosome consists of a highly structured RNA network formed between U2, U5 and U6 snRNAs and the conserved sequences in the pre-mRNA substrate. Little is known about the structure and function of proteins involved in the active site organisation. Among all spliceosomal proteins Prp8 stands out due to its size (280 kDa) and evolutionary conservation (61% sequence identity between yeast and human). Prp8 has been shown to be in close physical contact with the RNA catalytic core as well as numerous proteins, including GTPase Snu114 and DExD/H helicase Brr2, which are the key players in spliceosomal activation. I will present the crystal structure of yeast Prp8 (residues 885-2413) in complex with Aar2, a U5 snRNP assembly factor. The structure reveals tightly associated domains of Prp8 resembling a bacterial group II intron reverse transcriptase and a type II restriction endonuclease [1]. Suppressors of splice-site mutations, and an intron branch-point crosslink, map to a large cavity formed by the reverse transcriptase thumb, the endonuclease-like and RNaseH-like domains. Our structure provides first structural insights into the architecture of the spliceosome active site, and reinforces the notion that nuclear pre-mRNA splicing and group II intron splicing have a common evolutionary origin.

[1] Galej W.P., Oubridge C., Newman A.J., Nagai K. (2013). Nature 493:638-643.

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