

Cryo EM structure of yeast U1 snRNP offers insight into alternative splicing

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Pre-mRNA splicing is catalyzed by the spliceosome, a huge protein-RNA complex composed of the U1, U2, U4, U5, U6 snRNPs and many non-snRNP related proteins. Spliceosome is highly dynamic and undergoes dramatic compositional and conformational changes through the splicing cycle. U1 snRNP is critical for initial 5' splice site (ss) recognition and is a frequent target of the action of alternative splicing factors that either facilitate or prevent U1 snRNP from binding to 5' ss. Much of what we know today about the molecular mechanism and regulation of 5' ss recognition comes from genetic, biochemical, and structural studies of two commonly used model systems, *S. cerevisiae* (yeast) and human U1 snRNP. Intriguingly, the yeast U1 snRNP is much more complex than the human U1 snRNP. Yeast U1 snRNA is 3.5 times larger than its human counterpart and contains seven additional stably associated auxiliary proteins. In spite of the critical importance of yeast as a model system for understanding the mechanism of splicing that is often applicable to higher eukaryotes, there had been a lack of structural information of yeast U1 snRNP, despite the multiple high-resolution spliceosome structures solved recently. In contrast, much structural information on human U1 snRNP is available due to its compositional simplicity.

We have determined the structure of yeast U1 snRNP at 3.6Å resolution using cryo electron microscopy (cryo EM). The structure reveals for the first time the three-dimensional organization of yeast U1 snRNP, including common features as well as important differences from the human U1 snRNP. It provides atomic models of nearly all essential domains of U1 snRNA, all core proteins, and five auxiliary proteins (none of which has any prior structural information). The structure offers a framework to integrate a wealth of existing genetic and biochemical data regarding the structure and function of yeast U1 snRNP and the mechanism of 5' ss recognition. In addition, many of the yeast-associated U1 snRNP proteins have human homologs that weakly associate with the human U1 snRNP (hence not available in the human U1 snRNP structure) and are involved in alternative splicing. The yeast U1 snRNP structure and biochemical analyses based on the structure provided intriguing insight into the structure and function of these auxiliary human U1 snRNP proteins in alternative splicing in higher eukaryotes.