Atomic structure of *S. cerevisiae* 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. U1 snRNP is critical for 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* and human U1 snRNP. Intriguingly, the *S. cerevisiae* U1 snRNP is much more complex than the human U1 snRNP. *S. cerevisiae* U1 snRNA is 3.5 times larger than its human counterpart and contains seven additional proteins. In spite of the critical importance of *S. cerevisiae* as a model system for understanding the mechanism of splicing that is often applicable to higher eukaryotes, there has not been any structural information of *S. cerevisiae* 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 *S. cerevisiae* U1 snRNP at 3.7Å resolution using cryo electron microscopy (cryoEM). The structure reveals for the first time the three-dimensional organization of *S. cerevisiae* U1 snRNP, including common features as well as important differences from the human U1 snRNP. It provides atomic models of most of U1 snRNA and *S. cerevisiae*-associated 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 *S. cerevisiae* U1 snRNP and the mechanism of 5' ss recognition. In addition, many of the *S. cerevisiae*-associated U1 snRNP proteins have human homologs that weakly associate with the human U1 snRNP, and the *S. cerevisiae* U1 snRNP structure provides intriguing insight into the structure and function of these proteins in pre-mRNA splicing in higher eukaryotes.