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Structural basis of pre-mRNA splicing

The spliceosome catalyses the removal of the intron from nuclear pre-mRNAs and assembles initially into a pre-catalytic ensemble, termed complex B, which contains the snRNPs U1, U2 and the U4/U6.U5 tri-snRNP and numerous non-snRNP proteins. For catalytic activation the spliceosome undergoes a major structural rearrangement, mediated by the Brr2 RNA helicase, yielding the activated spliceosome (Bact complex). The final catalytic activation of the spliceosome requires an additional restructuring step by the RNA helicase Prp2. Using cryo electron microscopy we have investigated the 3D structure of the human U4/U6. U5 tri-snRNP complex and the yeast activated spliceosome. Our tri-snRNP model reveals how the spatial organization of Brr2 RNA helicase prevents premature U4/U6 RNA unwinding in isolated human tri-snRNPs and how the Sad1 protein likely tethers Brr2 to its pre-activation position. The structure of the yeast Bact complex reveals how the first step reactants (i.e., the 5' splice site and the branch site adenosine) are sequestered by protein prior to catalysis and provide insights into the molecular remodeling events that must be facilitated by Prp2 in order to generate a catalytically active spliceosome. In addition, comparison of the Bact spatial organization with the cryo-EM structures of the tri-snRNP reveal how many spliceosomal components are rearranged during activation of the spliceosome.

Biography

Reinhard Luhrmann has studied Doctorate with Professor Gassen from University of Münster (1973-1975), Postdoctoral fellow with Professor H. G. Wittmann at the MPI for Molecular Genetics, Berlin (1976-1980), and join as head of a Max Planck junior research group, Max Planck Institute for Molecular Genetics (1981-1988), as well as work for German Habilitation in biochemistry and molecular biology at the Free University of Berlin (1982), Professor for Physiological Chemistry and Molecular Biology at the University of Marburg (1988-1999). He is a Director and Scientific Member at the Max Planck Institute for Biophysical Chemistry, Honorary Professor at the University of Marburg (since 2000).

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