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Elucidation of the conformational dynamics of the spliceosome using small molecule inhibitors

Initiative: Konformationelle Kontrolle biomolekularer Funktionen (beendet)

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Pre-mRNA splicing is carried out by an elaborate ribonucleoprotein (RNP) complex, the spliceosome, which is assembled anew on each pre-mRNA intron by the stepwise interaction of snRNPs and multiple non-snRNP splicing factors. During its maturation into a catalytically active RNP, the spliceosome is repeatedly remodeled, undergoing multiple compositional and conformational changes. At present, only a limited number of spliceosome assembly/maturation intermediates can be distinguished, and they appear to represent a mixture of RNP conformational states. The specific inhibition of spliceosomal proteins that facilitate conformational changes in RNA and/or protein (e.g., spliceosomal helicases, PPIases or kinases) may enable the isolation of novel, conformationally homogeneous maturation intermediates of the spliceosome. It is thus planned to exploit small molecule inhibitors targeted at a particular enzyme to stall human spliceosomes at defined maturation states. Inhibitors will be identified using medium-throughput splicing or enzymatic assays, and rationally improved via crystal structure analysis of enzymes alone or complexed with inhibitors. 3D-structure probing of purified novel intermediates will be performed with pre-mRNA or snRNAs site-specifically labeled with chemical or fluorescent probes.

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