KOLLOQUIUM

Institut für Molekulare Biowissenschaften

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GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Science in progress

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Molecular basis of alternative splicing regulation through SRSF6 isoforms

The human serine-arginine rich splicing factor 6 (SRSF6) is part of the SR-protein family consisting of 12 members. SRSF6 is involved in (alternative-) splicing regulation and can itself exist in at least three isoforms. It is composed of an N-terminal RRM domain, followed by a pseudo RRM and a C-terminal serine-arginine rich disordered domain. With SRSF6 being an integral part of the splicing machinery, all three domains have been implicated in interacting with RNA and/or proteins, but individual interactions mediating SRSF6 specificity remain poorly understood. Therefore, our goal was to structurally and biochemically analyze single domains as well as their combinations to decipher their RNA interaction sites as well as their sequence requirements. To this end, we used nuclear magnetic resonance (NMR) spectroscopy combined with electrophoretic mobility shift assay, fluorescent polarization, and x-ray crystallography, applied to recombinant SRSF6 variants. In particular, we used RNA Bind-n-Seq to obtain RNA consensus motifs for the single and tandem RRMs. We found the two single RRMs to have significantly different binding affinities and sequence requirements towards RNA: RRM1 binds to cytosine- and adenine-rich RNAs in a canonical way, whereas RRM2 prefers purine-rich sequences in a non-canonical mode of interaction. To understand the latter on an atomistic level, we solved the crystal structure of RRM2 both in the apo- and RNA-bound forms, which confirm our NMR data in non-canonical RNA-binding mediated by RRM2's α-helix 1. Additionally, we found the linker between RRMs to play an important part in increasing affinity towards RNA in concert with RRM2.
Altogether, our data provide a strong structural basis for understanding the functions and target specificity of SRSF6 as opposed to the other 11 members of the SR protein family on a molecular level.

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More Information: https://tinygu.de/kolloqmbw