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Unearthing SRSF1's Novel Function in Binding and Unfolding of RNA G-Quadruplexes

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Abstract : SRSF1 governs splicing of over 1,500 mRNA transcripts. SRSF1 contains two RNA-recognition motifs (RRMs) and a C-terminal Arg/Ser-rich region (RS). It has been thought that SRSF1 RRMs exclusively recognize single-stranded exonic splicing enhancers, while RS lacks RNA-binding specificity. With our success in solving the insolubility problem of SRSF1, we can explore the unknown RNA-binding landscape of SRSF1. We find that SRSF1 RS prefers purine over pyrimidine. Moreover, SRSF1 binds to the G-quadruplex (GQ) from the ARPC2 mRNA, with both RRMs and RS being crucial. Our binding assays show that the traditional RNA-binding sites on the RRM tandem and the Arg in RS are responsible for GQ binding. Interestingly, our FRET and circular dichroism data reveal that SRSF1 unfolds the ARPC2 GQ, with RS leading unfolding and RRMs aiding. Our saturation transfer difference NMR results discover that Arg residues in SRSF1 RS interact with the guanine base but with other nucleobases, underscoring the uniqueness of the Arg/guanine interaction. Our luciferase assays confirm that SRSF1 can alleviate the inhibitory effect of GQ on gene expression in the cell. Given the prevalence of RNA GQ and SR proteins, our findings unveil unexplored SR protein functions with broad implications in RNA splicing and translation.

Keywords : SR, SRSF!, RNA G-quadruplex, unfolding, RNA binding
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