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Structural perspective on the Steroid Receptor RNA Activator, a ncRNA with potential implication in breast cancer.

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The steroid receptor activator gene encodes for both a non-coding (SRA RNA) and a coding RNA. The balance between the two species is important for the associated physiological effects. The SRA RNA and the encoded SRA protein (SRAP) are members of the diverse group of factors known as the nuclear receptor co-regulators. Although specific actions can be mediated by the encoded protein SRAP, the SRA RNA also has a proven action during hormone-mediated transcriptional responses. Understanding the specific association between the SRA RNA and these partners will provide critical tools to modulate hormone-mediated transcriptional responses. Increased understanding of these signalling pathways has great potentials for the development of synergistic treatments against breast and pancreatic hormone-responsive cancer for example. We are studying the specific association of the SRA RNA with the transcriptional regulator called the *SMRT/HDAC*-associated repressor protein (SHARP). The SHARP protein recruits the SMRT protein and histone deacetylases to the promoter regions, which in turn blocks the transcriptional machinery by promoting chromatin compaction. One issue is to understand how SHARP is brought to the transcription sites. The N-terminal region of SHARP contains three RRM domains (RRM2, RRM3 and RRM4) which are conserved within the entire protein family. We have obtained an atomic model of the N-terminal region of SHARP using X-ray crystallography. Two of these RRMs (RRM3-4) are forming a stable entity using a previously uncharacterized region. The RRM2 is associated to the others via a flexible helical linker. Small angle X-ray scattering experiments indicates that the linker could be used by the protein single RRM to reach two preferential orientations located on both side of the stable block formed by the RRM3-4. Furthermore, we characterized *in vitro* the binding properties of the RRM-containing protein fragment with their RNA binding sequences in the SRA RNA.

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