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Structural Basis of Pyrimidine-tract Recognition by the Essential pre-mRNA Splicing Factor U2AF.
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The essential splicing factor U2 Auxiliary Factor (U2AF⁶⁵) recognizes the poly-pyrimidine tract (Py-tract) pre-mRNA consensus sequence, and recruits the core splicing machinery to the 3' splice site during constitutive pre-mRNA splicing. Splicing repressors compete with U2AF⁶⁵ to regulate use of certain 3' splice sites. For example, Sex-lethal (SXL) specifically recognizes a Gua-containing Py-tract, whereas U2AF⁶⁵ prefers Ura-rich sequences. Nevertheless, U2AF⁶⁵, SXL, and other alternative splicing factors all recognize Py-tracts using tandem RNA Recognition Motifs (RRMs), one of the most common types of RNA binding domains. To understand how these seemingly similar proteins discriminate among a variety of Py-tracts, the structure of the U2AF⁶⁵ RNA binding domain (RRM1-RRM2) has been determined in complex with deoxy-uridine oligonucleotide at 2.6Å resolution. Numerous Ura-N3 and O4 contacts are consistent with the sensitivity of U2AF⁶⁵ to modifications at these positions. Surprisingly, similar hydrogen bond donors and acceptors are available for Gua recognition by SXL. Models with *tra* NSS Py-tract indicate that the bulkier Gua residue would be unlikely to fit on the surface of U2AF⁶⁵ without a dramatic change in the nucleic acid conformation.

