Emerging views of U2AF at the 3´ splice site: A disease-relevant step of gene expression

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Pre-mRNA splicing is a key step of gene expression and is frequently defective in inherited diseases and cancers. A heterodimer of U2AF1 and U2AF2 recognizes the 3´ splice site signals of pre-mRNAs and nucleates spliceosome assembly. We have shown by X-ray crystallography that U2AF2 recognizes nine pyrimidines (Py) of the splice site signal *via* tandem RNA recognition motifs (RRM1, RRM2) and integrated α-helical linkers. Complementary single molecule Förster resonance energy transfer (smFRET) and small-angle X-ray scattering experiments further demonstrate an ensemble of RRM1/RRM2 conformations, which converges on an inter-RRM FRET value consistent with the RNA-bound crystal structure following addition of a consensus Py tract RNA site. The structural role of the U2AF1 subunit for 3´ splice site recognition remains an outstanding question in the field. We find by smFRET that the presence of the full length U2AF1 subunit significantly alters the U2AF2 conformation. We suggest that the U2AF1-dependent U2AF2 structure explains the short, divergent Py tracts of sites that depend on U2AF1 for splicing. Further, such an influence on U2AF2 conformations may contribute to altered 3´ splice recogniton by a recurrent U2AF1 mutation of hematologic malignancies and lung cancers.