"Structural and Functional Definition of Posttranscriptional Regulatory Networks of Tumor-associated RNA-binding Proteins"

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Abstract: The molecular and cellular functions of the majority of RNA-binding proteins and their specific role in oncogenesis are poorly defined. Our objective is to study eight recognized tumor-associated RNA-binding proteins (RBPs), and define their target sites and regulatory function. This will provide a gene regulatory framework under which cancer-genome-related data are mined and studied. The Tuschl laboratory has developed a crosslinking technology for transcriptome-wide identification of RBP binding sites by incorporation of the photoreactive nucleoside 4-thiouridine (4SU) into mRNA of cultured cells. To establish a function of the RBP in transcript stabilization, degradation or alternative splicing, the identified sites are then correlated to changes in transcript levels from RBP overexpression and siRNA knockdown. In the course of the soft tissue sarcoma cancer genome project, the Singer laboratory identified an amplified genomic region centered over the RBPs IGF2BP1, IGF2BP2 and IGF2BP3 in dedifferentiated liposarcoma (DDLS) and well-differentiated liposarcoma (WDLS). To assess the specific roles of the IGF2BPs in liposarcomagenesis we plan to investigate the mRNA targets defined by the Tuschl laboratory in well-characterized DDLS and WDLS cells lines established by the Singer laboratory. To further understand the molecular basis of target RNA recognition, synthetic RNA comprising experimental or derived consensus binding sites and recombinantly expressed RBPs will be studied and the crystal structures determined by the Patel laboratory. This will provide insights into the molecular basis of disease-causing mutations and enable structure-based design approaches targeted to modulation/disruption of protein-RNA interactions.