Development of Chemotranscriptomics: Affinity-Based RNA Profiling for the Detection of Ligandable Interfaces of RNAs and RNA-Binding Proteins

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Abstract:
Affinity profiling for ligandable RNAs transcriptome-wide promises a means of unlocking the druggable transcriptome. Recent efforts toward probing ligandable RNA structural space employ various chemistry and custom bioinformatic techniques for target identification. However, these methods lack sensitivity as they primarily identify highly expressed transcripts and eschew the RNA binding proteins (RBPs) critical in constraining accessible RNA structures in-cellulo. Here-in, we present a method for interrogating ligandable RNA-RBP interfaces in-cellulo; calling upon bespoke multi-functional chemical probes to identify ligandable pockets at the junction of RNAs and RBPs transcriptome-wide. Through isolation and enrichment of probe-reactive biomolecules, our optimized affinity profiling method enables the identification of ligandable faces in RNAs through next-generation sequencing (NGS). We discuss technical optimizations, improved experimental controls, and adaptation of NGS-best-practices that will allow for affinity profiling to identify ligandable low-abundance transcripts in the non-coding transcriptome that are cell-state dependent.