

Presenter: Omar Mohsen Hedaya

Authors: Omar M. Hedaya, Feng Jiang, Kadiam Venkata Subbaiah, Li Xie, Jiangbin Wu, Darren Khor, Peng Yao

Title: CONTROLLING GENE EXPRESSION THROUGH RNA STRUCTURES OR ANTISENSE OLIGONUCLEOTIDES

Abstract

Studying the intricacies of gene expression is necessary to understand human health and advance therapeutic development to prevent and treat disease. Our lab focuses on understanding how mRNA translation is regulated by upstream open reading frames (uORFs), short peptide-encoding regions within the 5' untranslated region (5'UTR) of mRNA, which when translated results in the repression of the coding sequence (CDS) translation. We found that the presence of a double-stranded RNA (dsRNA) structure downstream of a uORF start codon promotes premature translation at uORFs and enhances this suppressive effect. The 5'UTR of the GATA4 mRNA, which encodes a transcription factor that regulates cardiac development and hypertrophy, was explored as a disease-relevant example of this mode of gene regulation. A double-stranded RNA region downstream of the GATA4 uORF promotes its activity, reducing cellular GATA4 protein levels. We found that this mechanism can be disrupted in cells using antisense oligonucleotides (ASOs) that prevent the formation of this dsRNA region. In contrast, ASOs designed to base-pair downstream of any ORF (e.g., uORF or CDS) to form an artificial bimolecular dsRNA structure enhance translation of that ORF. Following these paradigms, we can control whether a protein of interest is overexpressed or underexpressed in cells. In a proof-of-principle mouse study, we designed ASOs that promote the mouse GATA4 uORF activity. Mice injected with this ASO showed reduced cardiac GATA4 protein levels and resistance to cardiac hypertrophy. From this work, we found that RNA secondary structures can act as cis-acting regulatory elements that regulate mRNA translation. This knowledge inspired the development of novel ASOs that can serve as a tool for modulating protein levels in cells.