(2020-266) Protein Domains For Modulation Of Rna Stability And/Or Translation

Tech ID: 32558 / UC Case 2020-266-0

BACKGROUND

Existing art in modulation of gene expression by nucleic acid targeting mechanisms primarily comprises methods for REDUCING gene expression, e.g. via DNA targeting (CRISPR gene knockout, reduction of transcription via CRISPR-i), or RNA targeting (shRNAs/siRNAs, ASOs, microRNA mimics). ENHANCEMENT of gene expression on the RNA level has been achieved using microRNA inhibitors; however the effects are typically small and are not target-specific (many other microRNA target-RNAs are also upregulated).The molecular functions of the majority of RNA-binding proteins (RBPs) remain unclear, highlighting a major bottleneck to a full understanding of gene expression regulation.

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego have developed an invention that leverages recruitment, to 3' untranslated regions or coding regions, of RNA binding proteins (RBPs) to alter the stability and/or translation of a chosen target RNA.

The researchers developed a plasmid resource of 690 human RBPs that were subjected to luciferase-based 3'-untranslated-region tethered function assays to pinpoint RBPs that regulate RNA stability or translation. Enhanced UV-cross-linking and immunoprecipitation of these RBPs identifies thousands of endogenous mRNA targets that respond to changes in RBP level, recapitulating effects observed in tethered function assays. Among these RBPs, the ubiquitin-associated protein 2-like (UBAP2L) protein interacts with RNA via its RGG domain and cross-links to mRNA and rRNA. Fusion of UBAP2L to RNA-targeting CRISPR-Cas9 demonstrates programmable translational enhancement. Polysome profiling indicates that UBAP2L promotes translation of target mRNAs, particularly global regulators of translation. Our tethering survey allows rapid assignment of the molecular activity of proteins, such as UBAP2L, to specific steps of mRNA metabolism.

APPLICATIONS

Treatment of diseases where increased or decreased levels of specific proteins is of therapeutic benefit.

ADVANTAGES

This invention

(1) represents the first generalizable method to modulate gene expression in both directions,

CONTACT
Skip Cynar
scynar@ucsd.edu
tel: 858-822-2672.

OTHER INFORMATION

KEYWORDS

RNA-binding proteins, RBP, mRNA metabolism

CATEGORIZED AS

- Medical
  - Therapeutics
- Research Tools
  - Expression System
  - Protein Synthesis
  - Screening Assays

RELATED CASES

2020-266-0

(2) leverages both RNA stability and translation effects, and

(3) enables the magnitude and of the effect to be tailored by the type of RBP used as effector.

STATE OF DEVELOPMENT

In the instantiation provided in the publication cited below the researchers used MS2 tethering and a RNA-targeting CRISPR system to recruit the RBP to the target RNA (recruitment), used a reporter mRNA to measure changes in RNA stability and/or translation (target RNA), and delivered the system to cell lines by lipofection (delivery).

A person skilled in the art will be able to use other methods of recruitment (RNA-targeting CRISPR systems and artificial or natural sequence specific RNA binding proteins), other methods of delivery (virus-based delivery including AAV and lentivirus, to deliver the system into cells and live organisms), and other target RNAs (endogenous mRNAs, non-coding RNAs). They will able to identify and extract specific effector domains from the RBP sequences to reduce the size of the system.

INTELLECTUAL PROPERTY INFO

Patent-pending technology available for commercial development. US patent rights are available for licensing to interested parties.

The invention uses recruitment, to 3' untranslated regions or coding regions, of RNA binding proteins (RBPs) to alter the stability and/or translation of a chosen target RNA.

RELATED MATERIALS

▶ Luo EC, Nathanson JL, Tan FE, Schwartz JL, Schmok JC, Shankar A, Markmiller S, Yee BA, Sathe S, Pratt GA, Scaletta DB, Ha Y, Hill DE, Aigner S, Yeo GW. Large-scale tethered function assays identify factors that regulate mRNA stability and translation. Nat Struct Mol Biol. 2020 Oct;27(10):989-1000. doi: 10.1038/s41594-020-0477-6. - 08/17/2020

University of California, San Diego
Office of Innovation and Commercialization
9500 Gilman Drive, MC 0910, ,
La Jolla,CA 92093-0910

Tel: 858.534.5815
innovation@ucsd.edu
https://innovation.ucsd.edu
Fax: 858.534.7345