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Gene-specific enhancement of protein synthesis by targeting 5'UTRs -A novel oligonucleotide-based strategy for translational control of selected tumor suppressors

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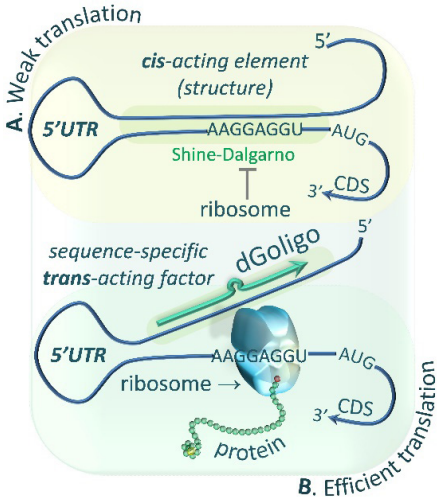
Background: The frequently reported lack of correlation between various mRNA and protein levels in cancers suggests that translational control can be an important target for new therapeutics regulating mechanisms of protein biosynthesis. Naturally occurring microRNAs and synthetic siRNAs are the most recognized regulatory molecules acting via RNA interference. Surprisingly, recent studies have shown that the interfering RNAs may also activate gene transcription via the newly discovered phenomenon of small RNA-induced gene activation (RNAa), triggered by promoter-specific small activating RNAs (saRNAs).

Findings: Here we show that oligonucleotide-based trans-acting factors termed dGoligos (dGs), which were designed by our dGenhancer calculator, can also specifically enhance gene expression at the level of protein translation by acting at sequence-specific targets within mRNA 5'-untranslated regions (5'UTRs) of THRB suppressor. The *in vitro* translation efficiency of reporter constructs containing alternative TRβ1 5'UTRs was increased by up to 55.8-fold following exposure to specific dGs. Complementary *in vivo* study showed that dGs can enhance TRβ1-5'UTR-mediated translation up to 4.8-fold. This method was successfully applied to enhance translation of another *CDKN2A* suppressor. Moreover, we show that the most folded 5'UTR has higher translational regulatory potential when compared to the weakly folded TRβ1 variant suggesting that the strategy may be especially applied to enhance protein synthesis from translationally non-active or less-active transcripts containing long complex 5'UTRs. dGs can serve as molecular switches to translationally active conformation of folded 5'UTRs leading to efficient translation of target mRNAs.

Significance: This study represent the first strategy for gene-specific translation enhancement using selective trans-acting factors designed to target specific 5'UTR cis-acting elements. This developmental strategy may complement other available methods for gene expression regulation including gene silencing and may find its use in enhancement of genes frequently silenced in cancers and other genetic disorders, especially at the level of translational control.



Biography

Adam Master has completed his Ph.D in medical sciences from The Center of Postgraduate Medical Education in Warsaw (medical biology), M.sc. from The Jagiellonian University in Krakow (molecular biology), Eng. from Krakow University of Technology (chemical technology, biotechnology of recombinant proteins). He has published 28 papers, more than 22 abstracts and 3 patents. In his work he has focused on translational control in cancer research, forensic sciences and genetic diagnostics in personalized molecular medicine. He is a member of The Polish National Chamber of Laboratory Diagnosticians, The American Society of Gene &Cell Therapy, and The British Society for Endocrinology.

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