Anton A Komar, J Mol Genet Med 2014, 8:3
http://dx.doi.org/10.4172/1747-0862.S1.001

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Genomics & Pharmacogenomics
September 08-10, 2014 DoubleTree by Hilton Hotel Raleigh-Brownstone-University, USA

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From genotype to phenotype: How and at what step of protein expression, mRNA translation affects protein folding in the cell?

Understanding the relationship between genotype and phenotype is one of the key questions in modern molecular biology. A very modest protein-transcript relationship exists in higher eukaryotes with only about 50% of all changes on the transcriptome level reflected on the proteome. The modest relationship between the proteins and transcripts can be explained by a number of reasons, including but not limited to alternative splicing, post-transcriptional control of gene expression, protein folding and modifications. A new paradigm that adds another level of complexity to our understanding of the relationship between genotype and phenotype is the effect of protein translation rates on protein folding. It has been postulated and shown that non-uniform kinetics of protein translation (which is mainly governed by non-uniform synonymous codon usage) can alter protein folding in the cell. It has been suggested that altered protein translation kinetics leads to altered appearance of the nascent polypeptide segments (emerging from the ribosome), leading to their altered co-translational folding. However, no direct evidence existed thus far, demonstrating altered conformation of the ribosome bound nascent chains due to altered elongation rates. Using a combination of different approaches, including but not limited to FRET, NMR and limited proteolysis, we have shown for the first time that kinetics of protein translation does affect the conformation of ribosome bound nascent chains. Eye lens protein Gamma-B crystallin was used as a model to demonstrate that altered synonymous codon usage leads to altered kinetics of translation and conformation of co-translational folding intermediates.

Biography

Anton A Komar is presently a Professor of Biology and the Director of the Center for Gene Regulation in Health in Disease (GRHD) at Cleveland State University (CSU), Cleveland, OH, USA. He also serves as the Director of the Cellular and Molecular Medicine Specialization (CMMS) Program, a doctoral program jointly operated by CSU and Cleveland Clinic Learner Research Institute. Komar also holds adjunct appointments at Case Western Reserve University (CWRU) School of Medicine and Cleveland Clinic Learner Research Institute. He received his PhD degree in Molecular biology from Lomonosov Moscow State University in 1991 and then (before coming to USA in 2001) worked in many different countries across the globe, including Germany, France and Switzerland. Dr. Komar is an accomplished investigator with extensive experience in the study of translational control of gene expression. He serves as an editorial board member of the journal “Translation” and was the editor of the 2nd edition of the “Single Nucleotide Polymorphisms: Methods and Protocols”, published by Springer/Humana Press.

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