Adaptive translation as a mechanism of stress response in biology

Awardee: Tao Pan
Award: Pioneer Award
Awardee Institution: University of Chicago

Co-authors: Michael Schwartz and Xiaoyun Wang
Co-author Institutions: University of Chicago

Genetic diversification is a fundamental requirement for adaptation to changing environments. This process is generally regarded to be time consuming and beyond the scope of the biochemistry within individual cells, which cannot deliberately alter their genetic code. However, recent evidence has revealed that cells can circumvent their genetic confines by making diversified proteins which do not strictly adhere to the amino acid sequence specified in DNA. This process is mediated by the incorporation of nongenetically encoded methionine residues in specific amino acid positions, which is accomplished by misacylation of nonmethionyl-tRNAs with methionine (1). Misacylation of non-Met-tRNAs with Met is highly regulated and can range from 0.01-10% of the Met-tRNAs charged with Met in the cell. Met-misacylation occurs in all three kingdoms of life. We hypothesize that “adaptive translation” can adapt the proteome of an organism for optimal function in varying environments and may be advantageous in conditions for which there is no effective transcriptional response. We are testing this hypothesis in all three branches of life. In *E. coli*, adaptive translation is regulated by specific post-translational modification of the methionyl-tRNA synthetase; chromosomal tRNA synthetases mutant strains that can no longer mischarge are deficient in responding to many types of environmental stresses. In an extreme archael thermophile, adaptive translation is regulated by temperature; Met-substituted mutant enzymes may perform better at the corresponding growth temperature. In human cells, we show that specific Met-substituted mutant enzymes can indeed show very distinct reactivities and cellular localization. Our investigation aims to establish that deviation from the central dogma has evolved to facilitate adaptation to varying natural conditions and in stress response.

(1) Netzer, Goodenbour et al.: *Nature* 462, 522-526 (2009).