Analysis of Upf Protein Over-Expression on the Efficiency of Targeting Aberrant mRNAs to NMD

Kazazic, Ella (School: Hathaway Brown School)

Quality control mechanisms exist throughout the gene expression pathway to ensure the accurate transmission of genetic information. Nonsense-mediated mRNA decay (NMD) is a translation-dependent quality control process that monitors the gene expression pathway for mRNAs harboring a nonsense mutation that directs premature translation termination. NMD elicits rapid degradation of these faulty mRNAs, preventing the accumulation of truncated proteins with potential deleterious effects to the cell. The proteins Upf1, Upf2, and Upf3 function in a complex to elicit rapid degradation of mRNA harboring a premature translation termination codon. The sensing model, a leading model to explain the mechanism of NMD, posits that the core NMD factor, Upf1, stochastically binds mRNA and is displaced by the translating ribosome as it moves along the open reading frame. The only sequence on which Upf1 accumulates, then, is downstream of the stop codon. Based on the model, the probability of a substrate being selected for NMD should be influenced by the length of RNA downstream of the stop codon and the cellular abundance of Upf1. In the ongoing work on this project, I am investigating whether NMD targeting efficiency can be increased by driving higher over-expression of the Upf proteins, and the requirement for the individual protein in driving more efficient NMD. The results from this ongoing work are consistent with previous results in which an overabundance of Upf1 alone was not sufficient to cause a marked decrease in NMD target abundance, despite Upf1 being over-expressed at even higher levels than previously tested. These results are likely due to Upf2 and Upf3 being expressed at physiological levels and being a rate-limiting step in NMD targeting in these cells.

Awards Won: