Interaction of unfolded protein and protein aggregates with the ribosome: Possible outcomes

Abstract

Ribosome is the cellular protein synthesizing machine that plays a role in determining the proteome of the cell. Amongst the many known non-canonical roles of the ribosome, the ability to act as an ATP independent chaperone has significant cellular relevance, especially during times of stress when the ATP dependent chaperoning machinery of the cell is rendered paralysed. Interestingly, the unfolded protein needs to be present at a stoichiometric amount with respect to the ribosome. However, when the protein is present at a five-fold excess, it acts as an anti-association factor, preventing reassociation of the ribosomal subunits. Our current studies discussed in **Chapter 2** show that the basis for this anti-association activity is its sustained association with 50S ribosomal subunit. This phenomenon generates a sustained pool of dissociated ribosomal subunits which become prone to degradation by cellular nucleases. Partially unfolded states of the protein like the molten globule intermediate can also successfully dissociate the ribosome. During stressful circumstances when there is a global rise in unfolding of the proteome, the possibility of losing the ribosomal population to unfolded protein mediated dissociation and degradation can prove to be a serious threat to cellular survival. During such circumstances, ribosome associated stress factors like YfiA are expressed which form translationally hibernating ribosomes. Our studies with YfiA reveal that it can successfully protect the ribosome from unfolded protein mediated dissociation and subsequent degradation, while preserving the ribosome's ability to act as an ATP independent chaperone. Our further studies, discussed in **Chapter 3** deal with a different aspect of ribosome-unfolded protein interaction, where the concentration of the protein is remarkably higher (100-fold excess) with respect to the ribosome. Previous investigations in the laboratory conducted primarily with the lysozyme protein revealed that in such a scenario, when ribosome is present in the vicinity of amorphously aggregating system, it gets sequestered into large insoluble RNA-protein co-aggregates. The human Tau protein is a major constituent of neurofibrillary tangles found in Alzheimer's disease neurons. Our current observations with the full-length Human Tau protein (Ht40) and its microtubule binding subdomain (K18) show that amyloid forming intrinsically unstructured proteins can also destroy the ribosomal physical as well as functional integrity by sequestering the ribosomal components into large and small rRNA-protein co-aggregates. Hence, targeting of the cellular translational machinery, might be a possible mechanism of tau aggregate mediated neurotoxicity.