“EnTRAPped Ribosomes: TRAP is a Unique Mechanism to Maintain Protein Homeostasis via Sequestering Malfunctional Ribosomes into Protein Quality Control Compartment”

To keep protein synthesis efficient, cells need to monitor the functionality of their ribosomes and eliminate those that fail to perform well in translation. Previous studies have shown that yeast ribosomes containing mutations in the core structural regions of their rRNAs (Decoding Center or Peptidyl Transferase Center), and therefore incapable of supporting protein synthesis, become substrates of Non-functional rRNA Decay (NRD), a pathway that leads to their rapid degradation. However, our knowledge is still very limited about the fate of ribosomes that harbor mutations or suffer environmental damage in the non-core, auxiliary regions. These ribosomes, although capable of translating a message, may be compromised in functions such as interactions with the post-translational protein-folding machinery, nascent chain modification enzymes, and factors performing protein quality control. In this study, we focused on the eukaryote-specific expansion segment 7 (ES7) of the large ribosomal subunit rRNA, a region that does not have a known essential role in protein synthesis but was previously implicated in cellular stress responses. We identified a set of mutations within the ES7 region of the yeast ribosome that does not affect the production of mature and translationally active large ribosomal subunits, yet were unable to support cell growth, likely due to mRNA decoding defects. Our study showed that these mutated ribosomes are not substrates of NRD. Unlike NRD substrates that undergo fast decay, ES7 mutants were stable. Instead, these ribosomes were present in cytoplasmic foci shared with misfolded soluble proteins (JUNQ foci). We provide a working model wherein the entire complexes of ribosomes associated with aberrant nascent chains or polypeptides (defective in cotranslational folding due to ES7 mutations), move into cytoplasmic compartments enriched in factors that perform nascent chains refolding or target them for degradation. We propose that this pathway, termed TRAP (for Translational Relocalization with Aberrant Polypeptides), is a cellular strategy to maintain protein homeostasis. As such, besides facilitating the accommodation of proteins’ native state, TRAP may also help to keep translation at its peak efficiency by preventing malfunctioning ribosomes from immediately returning to active duty in translation. These results shed new light on the interplay between protein and ribosome quality control mechanisms in maintaining cellular homeostasis. Our study provides an essential platform for better understanding the etiology of human diseases, such as neurodegeneration, and may help in developing new therapeutic strategies.