Error-free translation as a novel therapeutic approach against age-related neurodegenerative diseases

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The accumulation of protein aggregates plays a central role in the development of many neurological disorders such as Alzheimer's or Parkinson's disease. Protein misfolding, malfunction, and aggregation are connected to the accuracy of gene expression where protein translation is the most error-prone step. Translation errors lead to misfolding of proteins, thus contributing to progression of protein aggregation-related diseases. We have shown that increasing error frequency with specific point mutation (ram, ribosomal ambiguity) in the ribosomal protein RPS9 leads to general premature aging and age-related neurological disorder recapitulating early symptoms of Alzheimer's disease in mice. We propose to reduce the amount of erroneously translated proteins by increasing protein translation fidelity. We have identified some genetic and pharmacological interventions decreasing translation errors and demonstrated that increased fidelity of protein biosynthesis restores proteostasis and reduces protein aggregation in basic cell culture models. As a further step of validation, we plan to use more appropriate experimental model(s) such as mouse neuronal cells and PD patient-derived iPS cell lines.