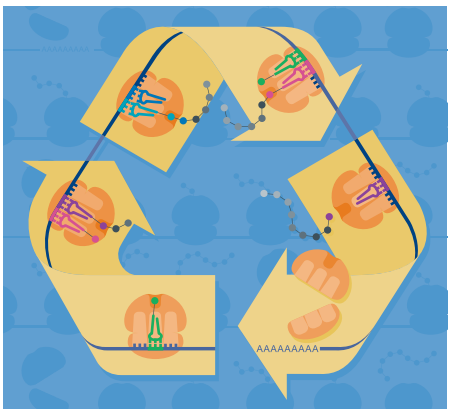
Protein translation

# Translation feedback control in the brain




Translation occurs in three steps: initiation, elongation and termination. Defects in translation elongation can result in toxic aggregation-prone and non-functional proteins that are implicated in many diseases including neurodegeneration. A foundational study by the Ackerman lab (Ishimura et al., 2016) demonstrated that impaired translation elongation promotes the repression of translation initiation, and that this feedback control has an important role in brain health. The group had previously found that ribosome stalling in mice, caused by deficiencies in the ribosome rescue factor *Gtpbp2* and the nervous-system-specific $tRNA^{Arg}_{UCU}$ genes, leads to ageing-associated neurodegeneration (Ishimura et al., 2014). Excitingly, their 2016 study revealed that ribosome stalling in this context causes a neuroprotective suppression of translation initiation in the brain that delays the onset of neurodegeneration. Without this reduction in translation initiation, the authors demonstrate a profound acceleration and escalation of neuronal loss in the brain. I highlight three major implications of this study that, in my opinion, are the roots of now flourishing branches of the proteostasis field.

First, the authors demonstrated that ribosome stalling leads to suppression of translation initiation via the integrated stress response. The integrated stress response occurs when stress-sensing kinases phosphorylate the translation initiation factor eIF2α. Phosphorylation of eIF2α reprogrammes gene expression by suppressing translation initiation while promoting the expression of stress-induced genes. Research from many labs has shown that ribosome stalling impairs nascent protein synthesis and causes mRNA decay. Ishimura et al. (2016) substantially extended our knowledge of how stalled ribosomes are sensed and cause global changes in gene expression via the integrated stress response. This research set the stage for a highly active area of research on the feedback mechanisms that link each step of the mRNA translation cycle.

Second, this study suggested that the eIF2α kinase GCN2 can be activated by stalled ribosomes. Earlier work had demonstrated that uncharged tRNAs activate GCN2 by preferentially binding its histidyl-tRNA synthetase-like domain. Ishimura et al. showed that phosphorylation of eIF2α was dependent on GCN2, as were more than half of the gene expression changes observed in the cerebella of mice deficient in *Gtpbp2* and $tRNA^{Arg}_{UCU}$. However, the uncharged:charged $tRNA^{Arg}_{UCU}$ ratio was not altered in mutant *Gtpbp2* and $tRNA^{Arg}_{UCU}$ mice, strongly suggesting that activation of GCN2 after ribosome stalling did not depend on uncharged tRNAs. This paradigm-shifting idea sparked a flurry of studies to identify the molecular mechanisms of GCN2 activation by ribosome stalling.

Third, Ishimura et al. demonstrated that GCN2 has a protective effect in the context of neurodegeneration associated with ribosome stalling. Deletion of *Gcn2* (also known as *Eif2ak4*) worsened locomotor function and cerebellar pathology in *Gtpbp2*- and $tRNA^{Arg}_{UCU}$-deficient mice. The integrated stress response may have a neuroprotective role by limiting translation initiation to prevent further ribosome stalling events, reduce aberrant protein production, and promote the expression of pro-survival stress-induced genes. Thus, this study provided strong evidence for the therapeutic potential of modulating the integrated stress response to prevent or treat neurodegeneration.

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