COMMENTARY

Translation dysregulation in neurodegenerative disorders

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Aberrant translational repression has emerged as a common feature across multiple neurodegenerative disorders. The mechanisms underlying translational repression have not been fully elucidated but, in some cases, involve activation of the integrated stress response (ISR) pathway by disease-associated, aggregation-prone proteins. For example, studies in mouse models of prion and tauopathy disorders demonstrate a link between expression of misfolded forms of prion and tau proteins, respectively, and phosphorylated alpha subunit of eukaryotic initiation factor 2 (p-eIF2α)-dependent translational repression. Remarkably, disease-related phenotypes are alleviated in these models by pharmacological and genetic interventions that restore protein translation (1, 2). What do we know about translational repression in the context of amyotrophic lateral sclerosis (ALS) and related disorders such as frontotemporal dementia (FTD)? A new report in PNAS by Kamelgarn et al. (3) addresses this question by contributing mechanistic insight into how the ALS- and FTD-associated protein fused in sarcoma (FUS) modulates translation during disease. Interestingly, these authors found that the effects of mutant FUS on translational repression extend to the nonsense-mediated decay (NMD) pathway. These findings reinforce the notion that translation dysregulation plays a role in neurodegenerative disease pathogenesis and highlight the factors involved in NMD as therapeutic targets for these disorders.

ALS-FUS Affects Multiple Aspects of Translation

FUS is an RNA/DNA-binding protein that shuttles between the nucleus and cytoplasm and engages in diverse cellular processes that include transcription, splicing, and translation (4). A majority of ALS-linked mutations are located within the nuclear localization sequence and cause the protein to accumulate and ultimately aggregate within the cytoplasm (5, 6). Notably, FUS dysfunction is relevant to other forms of neurodegeneration, as cytoplasmic FUS pathology has been detected in some cases of sporadic ALS and FTD without FUS mutations (6, 7). Kamelgarn et al. (3) devised a clever approach for isolating these mutant FUS-containing cytoplasmic inclusions for downstream proteomics analyses using mass spectrometry. Gene ontology assessments of the proteins identified in the FUS-containing inclusions revealed protein translation-relevant terms, including the ribosomopathy Diamond–Blackfan anemia that manifests with diminished protein synthesis (3). These correlations provided a clue that protein translation could be perturbed by the presence of FUS-containing inclusions. Indeed, multiple factors that are critical for protein translation colocalized within cytoplasmic inclusions containing mutant FUS in primary neurons. Kamelgarn et al. then employed several translation-based assays to demonstrate that protein translation was in fact reduced in cells expressing ALS-linked mutant forms of FUS, including in patient-derived fibroblast lines that express endogenous levels of FUS. These observations are consistent with a previous study that identified reduced protein synthesis in growth cones of cultured *Xenopus* retinal ganglion neurons expressing mutant FUS proteins (8). Recently, near-endogenous levels of mutant FUS were shown to activate the ISR, thereby triggering translational repression in a humanized FUS mouse model of ALS (9). In humanized FUS mice, translational repression does not require overt cytoplasmic FUS aggregation, but rather involves down-regulation of genes encoding ribosomal proteins and up-regulation of eIF2α signaling (9). While it appears that expression of mutant FUS can promote translational repression through multiple mechanisms (3, 9), mutant FUS has also been shown to enhance protein translation within specific types of RNA granules that localize to cell protrusions (10). Therefore, the relationship between FUS and translation is complex and likely to be context dependent.

Targeting the NMD Pathway in Disease

Kamelgarn et al. (3) delved deeper into the association between mutant FUS expression and translational repression. The authors confirm that mutant FUS does not interfere with translation initiation but likely causes an accumulation of prematurely terminated

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Author contributions: D.A.B. wrote the paper.
The author declares no conflict of interest.

See companion article on page E11904.
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Published online November 30, 2018.

www.pnas.org/cgi/doi/10.1073/pnas.1818493115

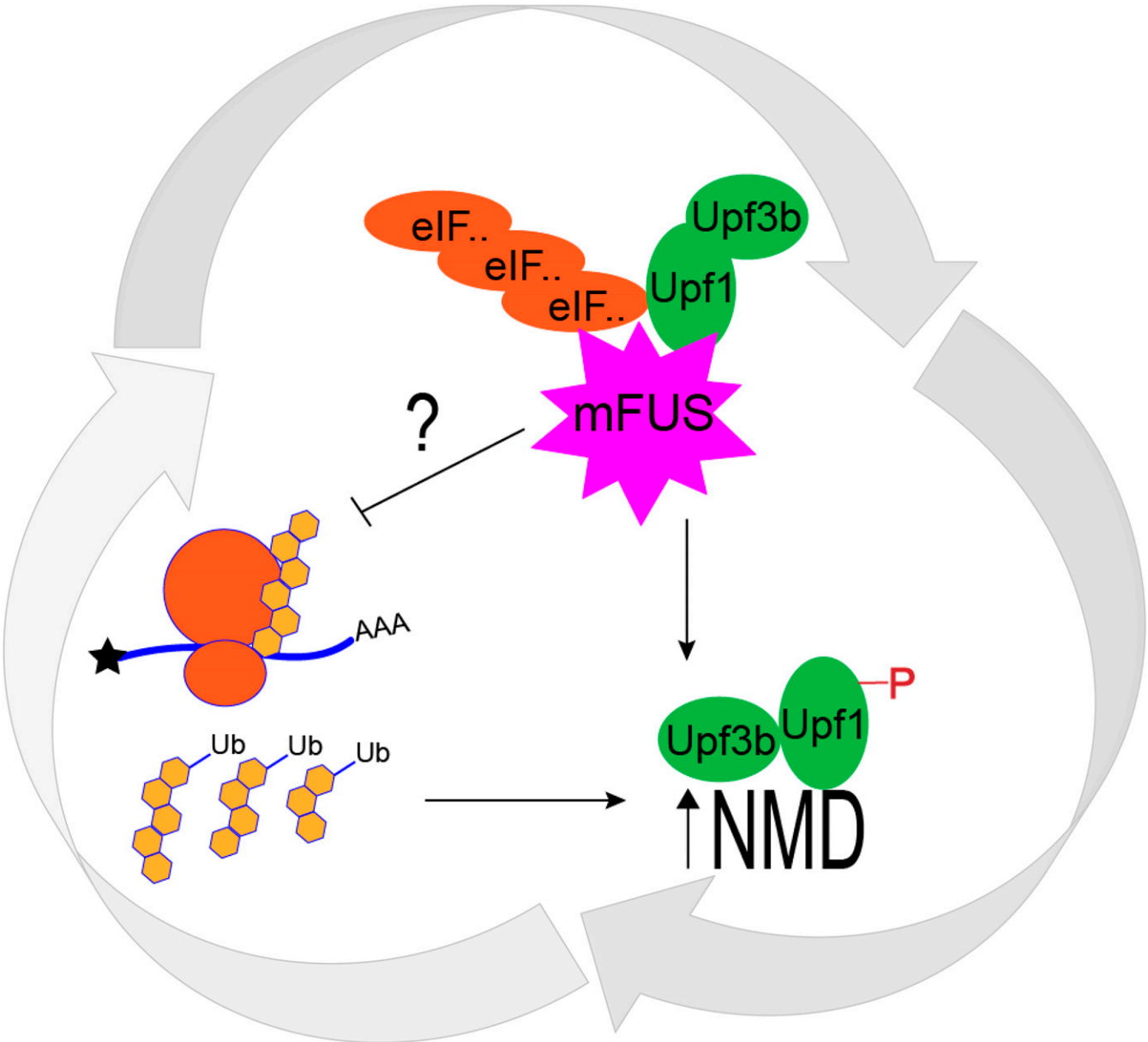

Fig. 1. A vicious cycle of translation dysregulation. Expression of ALS-linked mutant FUS (mFUS) leads to the accumulation of prematurely terminated proteins through a mechanism that has not been fully elucidated but that may involve the sequestration of translation eIFs within cytoplasmic FUS inclusions. Premature translation termination is thought to activate the NMD pathway. Aberrant binding and sequestration of NMD-associated factors by mutant FUS is thought to further exacerbate NMD activation and interfere with autoregulatory features of this pathway. The blue line represents an mRNA transcript that is being translated into protein (linked hexagons). The mRNA has a 5′ cap (denoted by black star) and poly-A tail. AAA, poly-A tail; P, phosphorylation; Ub, ubiquitination.

polypeptides. Supporting this notion, the authors discovered that factors involved in the mRNA degradative pathway, known as NMD, were up-regulated in mutant FUS-expressing cells compared with controls. The NMD pathway targets mRNAs with premature stop codons for degradation and removes mRNA encoding truncated or prematurely terminated proteins (11). As one might expect, defects in NMD are linked to various human diseases (11). Kamelgarn et al. (3) show that levels of the NMD-activating proteins up-frameshift (UPF)1 and UPF3b were elevated in mutant FUS-expressing cells at both the mRNA and protein levels, while negative regulators of NMD, such as UPF3a, were reduced (3), consistent with enhanced activation of the NMD pathway. Results from NMD-reporter constructs and quantification of endogenous NMD substrates provide further evidence that NMD is hyperactivated in mutant FUS-expressing cells. Curiously, while multiple NMD substrates were reduced in mutant FUS-expressing cells (consistent with NMD hyperactivation), those transcripts encoding the NMD factors themselves were spared. These data hint at a disruption of the normal autoregulatory mechanisms that control NMD activity and keep mRNA turnover in check (12). Indeed, Kamelgarn et al. (3) show that enhanced binding between mutant FUS and UPF1 proteins correlated with reduced binding between UPF1 protein and UPF1 mRNA, presumably accounting for elevated levels of UPF1 mRNA and protein in mutant FUS cells. Collectively, the results obtained by Kamelgarn et al. suggest a model whereby mutant

FUS causes dysfunctional protein translation that in turn activates the NMD pathway. Mutant FUS exacerbates this cycle by interfering with NMD autoregulation (Fig. 1).

Is it possible to counteract NMD hyperactivation? Kamelgarn et al. (3) propose that overexpression of NMD-related factors may reset the NMD autoregulation circuit (12). While forced expression of NMD-related factors may seem counterintuitive since UPF1 is already elevated, overexpression of the UPF1 helicase protein was in fact shown to significantly rescue mutant FUS toxicity in several model systems, including yeast (13) and primary neurons (14). UPF1 overexpression was also neuroprotective in a rodent model of TAR DNA-binding protein (TDP-43) toxicity (15). Like FUS, TDP-43 is an RNA-binding protein involved in both ALS and FTD pathogenesis (6). Interestingly, modulating the NMD pathway with nonsense-codon suppressors, which allow read-through of the stop codon by the translational machinery, has already demonstrated clinical utility for several human diseases that manifest from diminished protein expression (16). Whether the reported therapeutic effects of UPF1 in models of ALS/FTD are directly related to NMD remains to be determined, as UPF1 also has functions outside the NMD pathway (17).

Outlook

The study by Kamelgarn et al. (3) adds to a growing body of evidence that translational repression is involved in neurodegenerative disease pathogenesis (1–3, 9, 18). Whether mutant FUS-induced translational repression is an upstream trigger of ALS/FTD or represents a consequence of the disease course has yet to be demonstrated. Further, the mechanism(s) for exactly how mutant FUS induces translation-related defects is unclear. It will also be important to know exactly which proteins are translationally repressed and whether these are the same proteins across different neurodegenerative disorders. In addition to FUS, there are several other ALS/FTD-linked RNA-binding proteins that misfold and have the potential to impair RNA processing (19), raising the possibility that aberrant translational repression and dysfunctional NMD are more widespread in disease than is currently thought. Given the therapeutic efficacy of drugs that target the ISR and alleviate translational repression in different models of neurodegeneration (1), there is optimism that these compounds could also be beneficial in models of ALS/FTD (9, 15, 18).

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