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RNA Degradation in Neurodegenerative Disease

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Abstract

Ribonucleic acid (RNA) homeostasis is dynamically modulated in response to changing physiological conditions. Tight regulation of RNA abundance through both transcription and degradation determines the amount, timing, and location of protein translation. This balance is of particular importance in neurons, which are among the most metabolically active and morphologically complex cells in the body. As a result, any disruptions in RNA degradation can have dramatic consequences for neuronal health. In this chapter, we will first discuss mechanisms of RNA stabilization and decay. We will then explore how the disruption of these pathways can lead to neurodegenerative disease.

Keywords

RNA; decay; alternative splicing; transport; stress granule; exosome; disease; neurodegeneration

Mechanisms to Maintain RNA Stability

Following transcription, the newly formed transcript can be stabilized in several ways (Fig. 1). Most RNA that codes for protein, also referred to as coding or messenger RNA (mRNA), undergoes several processing steps that prevent degradation, assist in export from the nucleus, and aid in translation. Additionally, both coding and non-coding RNA (ncRNA) are stabilized by the adoption of unique secondary structures or sequestration in cytoplasmic ribonucleoprotein particles when the cell is under stress.

Polyadenylation

Polyadenylation refers to the addition of a series of adenosine monophosphates to the 3' end of mRNA transcripts [1]. This poly(A) tail protects nascent mRNA from enzymatic degradation [2,3], facilitates nuclear export [4], and assists in translation [3]. Polyadenylation begins when a complex of several proteins recognizes a binding site on the mRNA transcript. An enzyme in this complex, cleavage/polyadenylation specificity factor (CPSF), cleaves the 3' end of the transcript, and a second component, polyadenylate polymerase, adds sequential adenosine monophosphate units to create the poly(A) tail [5]. As the poly(A) tail grows longer, polyadenylate binding protein 2 (PAB2) is recruited, which further increases the affinity of polyadenylate polymerase to the RNA [6]. Additional

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poly(A)-binding proteins then associate with the tail and facilitate nuclear export, stabilization of the RNA, and translation [7].

Many transcripts harbor more than one polyadenylation site. The site that is ultimately utilized primarily affects the length of the 3' untranslated region (UTR), with little direct influence on protein translation or function [8]. However, the 3'UTR may also encode microRNA recognition elements [9], DNA methylation sites [10], or motifs recognized by regulatory RNA-binding proteins [11,12]. Thus, where a poly(A) tail starts can significantly influence the likelihood of transcript degradation. Moreover, in some cases alternative poly(A) binding sites occur within the coding region, and their usage results in truncation of the translated protein [13]. Poly(A) tails are gradually eroded over time, and transcripts with shorter tails are both less likely to be transcribed and more likely to be degraded [14]. This process can be accelerated by the binding of microRNA to the 3' UTR or through the removal or degradation of poly(A) binding proteins [15].

Methylguanine Cap

The majority of coding RNAs undergo a second processing step that involves the addition of a methylguanine cap to the 5' end of the transcript. This cap stabilizes the transcript by preventing exonuclease-mediated degradation [16–18], and is also required for the translation of most mRNAs [19,20]. Additionally, the 5' cap assists in splicing [21–25], nuclear export [24,25], and possibly polyadenylation [26].

The capping process is initiated before transcription is complete, and begins when RNA triphosphatase removes one of the 5' terminal phosphate groups [27]. mRNA guanylyltransferase then catalyzes the addition of guanosine triphosphate to the remaining terminal biphosphate to create an unusual 5' to 5' triphosphate linkage. This guanosine is then methylated by a methyltransferase [27]. The cap binding complex (CBC) binds to the methylated 5' cap, which is in turn recognized by the nuclear pore complex and exported into the cytoplasm [28,29]. Once there, the CBC is replaced by the translation factors eIF4E and eIF4F, which are recognized by other translation initiation machinery components, including the ribosome [30,31].

Binding of the CBC and translation factors also stabilize transcripts by blocking the binding of decapping enzymes [32–34]. When these decapping enzymes outcompete the translation factors, they hydrolyze the 5' cap and expose the 5' monophosphate. The resulting decapped transcripts are subject to rapid degradation by 5' exonucleases [35].

Secondary Structure

DNA primarily forms double helices, but the single stranded nature of RNA and its propensity to form hydrogen bonds allows it to form more complex structures that can directly affect transcript stability. The most common RNA secondary structure is the hairpin loop, created when two complementary regions of the same strand base-pair to form a double helix that ends in an unpaired loop [36]. These loops are found in pre-microRNA, transfer RNA (tRNA), and mRNA, and their stability depends on several factors, including length, degree of complementarity in the stem, and guanine to cytosine base pair content.

Hairpin loops stabilize mRNA [37–40] and in many cases increase translation efficiency [39,40]. This may occur by blocking exonuclease activity, but the precise mechanism remains unclear. Hairpin loops may also act as binding sites for proteins that direct mRNA transport and localization [41–43].

The combination of several hairpin loops forms a multiloop; the most abundant example of this structure is found in the cloverleaf-shaped tRNAs that assist in protein translation. The relative stabilities of multiloops vary based on size, number of loops, and complementarity [44]. Hairpin loops can also form pseudoknots, in which at least two hairpin loops are linked by single stranded loops. Pseudoknots are relatively stable, and though little is known about their functional significance, they form the catalytic core of some ribozymes [45,46] and telomerases [47] and may also be involved in translation [48]. Other structures, such as G-quadruplexes and R-loops, are more often associated with disease and will be discussed below.

Stress Granules

Cells undergo a wide range of molecular changes in response to environmental stressors, including the inhibition of conventional translation [49,50] and the formation of stress granules (SGs), cytoplasmic ribonucleoprotein particles rich in mRNA, RNA-binding proteins, and stalled translation initiation complexes [51–53]. SG coalescence effectively sequesters the attached mRNAs and the 40S ribosome subunit [54,55], preventing further translation and stabilizing the bound mRNAs. Proteins unrelated to the original translation initiation complex are also recruited, and their composition helps determine SG dynamics and longevity [56]. Which proteins participate is often dependent on their posttranslational modifications and the specific stressor involved [57–61], providing a rapid and reversible way for the cell to modulate SG formation and composition. Many RNA-binding proteins found in SGs contain low-complexity domains that are inherently flexible; the ability of these domains to form reversible homo- and heterotypic interactions with one another via their low-complexity domains may be responsible for the dynamics of SG formation and dissociation [62,63]. Additionally, SGs often contain a number of proteins that promote RNA stability and regulate translation [64]. Moreover, deadenylation is largely inhibited in stress granules [65–67]. When the stressor has passed, several RNA-binding proteins catalyze SG disassembly [68–70], and the transcript is either degraded or released to resume translation. These observations suggest that SGs serve two basic functions: preventing the translation of unnecessary transcripts during stress, and protecting these transcripts from degradation until the stress has subsided.

Mechanisms of RNA Decay

The typical life of an mRNA transcript includes a complex sequence of events including transcription, capping, adenylation, splicing, and export. When mistakes occur during this process, quality control mechanisms exist to recognize and eliminate defective transcripts that may give rise to dysfunctional or toxic proteins (Fig. 1). However, these pathways do more than ensure the fidelity of RNA transcripts. They also serve important regulatory roles,

enabling rapid modulation of steady-state RNA levels—and therefore protein production—in response to changes in the intracellular or extracellular environment.

RNA Degradation Machinery

There are three major classes of intracellular RNA-degrading enzymes: endonucleases that cut RNA internally, 5' to 3' exonucleases that degrade RNA from the 5' end, and 3' to 5' exonucleases that hydrolyze RNA from the 3' end. These enzymes may work independently or within a complex such as the exosome, a versatile structure for the degradation of immature or abnormal RNA. The core of the eukaryotic exosome complex is formed by nine proteins, six of which are members of the RNase PH-like family [71]. These form a ring that is capped by three additional proteins with RNA-binding domains [72]; this structure bears remarkable similarity to the 26S proteasome [73], which consists of a central proteolytic barrel (the 20S core) capped on either end by 19S regulatory subunits. The exosome is primarily composed of 3'–5' exoribonucleases, and RNAs are degraded by removing terminal nucleotides from the 3' end of the transcript. This occurs through the cleavage of phosphodiester bonds, either through RNase PH-like protein-mediated phosphorolytic cleavage or hydrolytic cleavage by proteins associated with the exosome [74]. Several other proteins bind to the exosome to regulate its activity and specificity [75–77]. The exosome also processes small nuclear RNAs, small nucleolar RNAs, and ribosomal RNAs [78], though how these molecules are targeted to and released from the exosome remains unclear.

Nonsense-mediated Decay

Occasionally, errors introduced during transcription, insertions, deletions or nonsense mutations uncover premature stop codons (PTCs) within the coding sequence of an mRNA. If translated, PTC-containing transcripts would encode truncated proteins that may have toxic gain-of-function or dominant-negative activities. Nonsense-mediated decay (NMD) is a surveillance mechanism that eliminates transcripts containing PTCs, thereby preventing the synthesis of proteins that could be detrimental to the cell.

mRNA transcripts undergo splicing following transcription, during which introns are removed and exons are spliced together. The resulting exon exon junctions (EEJs) are occupied by a complex of proteins (the exon junction complex, or EJC) that assist in splicing until they are displaced by the ribosome during the first, or pioneer, round of translation. If the stop codon is downstream or within about 50 nucleotides of the final EJC, the transcript is translated normally. According to the EJC model of NMD, a stop codon that occurs upstream of an EJC is recognized as a PTC, triggering transcript degradation [79,80]. When the ribosome stalls at a PTC, the protein UPF1, along with the eukaryotic release factors eRF1 and eRF3, form the surveillance complex (SURF) and bind adjacent to the PTC. SURF then interacts with two components of the nearby EJC, UPF2 and UPF3B [81–83]. This triggers UPF1 phosphorylation, which causes the complex to move along the mRNA, resolving secondary structure and removing adherent proteins that may inhibit degradation [84,85]. Phosphorylated UPF1 also binds to SMG6, an endonuclease that directly cleaves the mRNA [86,87], as well as SMG5 and SMG7, which trigger deadenylation [88], decapping, and further degradation [89]. Additionally, UPF1 may be recruited to transcripts

independent of a PTC or adjacent EJC, particularly within long 3' UTRs. [90]. A working theory is that UPF1 preferentially binds long 3' UTRs and is phosphorylated via an unknown mechanism, triggering transcript decay. However, more work is required to identify the pathway resulting in destabilization of transcripts bearing long 3'UTRs.

Alternative Exon Inclusion and Exclusion

Though NMD is an important quality control mechanism, it also helps regulate the expression of functional mRNA [91], predominantly through alternative mRNA splicing. This phenomenon is remarkably widespread: NMD-related regulation of transcript abundance is involved in cell proliferation [92,93], immunity [94], stress [95], viral response [96], and neuronal activity [97,98]. The differential inclusion or exclusion of exons (alternative splicing) enables a single gene to encode multiple transcript and protein isoforms, and in many cases alternatively spliced transcripts are subject to NMD. Because changes in the splicing environment determine which isoforms are produced [99,100], alternative splicing can regulate gene expression by creating transcripts that are more or less stable. An estimated 33% of alternative transcripts contain PTCs [101], and between 12% and 45% of alternatively spliced transcripts are estimated to be NMD targets [101]. Regulated unproductive splicing (RUST) of this type regulates RNA abundance in relation to neuronal activity levels [102], developmental stage, and cell type [103]. Moreover, there is growing evidence that RUST is utilized by several RNA-binding proteins to regulate their own expression (autoregulation), particularly components of the splicing machinery [104–108].

Upstream Open Reading Frames

Upstream open reading frames (uORFs) are mRNA elements that include a start codon in the 5' UTR that is out-of-frame with the main coding sequence. Because ribosomes bind to the 5' cap of the mRNA and scan for start codons, uORFs can disrupt or interfere with translation of the downstream coding sequence [109,110]. Moreover, any stop codon at the 3' end of the uORF resembles a PTC within the context of the whole transcript. As predicted by the EJC model of NMD, the presence of uORFs correlate with lower expression levels of the downstream ORF [111,112], and uORF-bearing transcripts are particularly susceptible to degradation by NMD [113–115].

Nonstop Decay

Nonstop decay (NSD) is a surveillance mechanism involved in the detection and degradation of mRNA transcripts that lack stop codons [77,116] due to premature polyadenylation or point mutations that disrupt existing terminal codons. Without a recognizable stop codon, the ribosome translates into the poly(A) tail and then stalls, unable to release the mRNA transcript [117].

NSD is activated when Ski7, a component of the exosome complex, binds the empty aminoacyl (A) site of the stalled ribosome via its C-terminal domain [76,77]. This is supported by the fact that C-terminal deletions of Ski7 result in impaired NSD but do not

affect general exosome function [116]. Additionally, the Ski7 C-terminal domain strongly resembles other proteins that bind the ribosome during normal translation, elongation, and termination such as EF1a and eRF3 [118]. After binding, Ski7 releases the stalled ribosome and recruits the exosome to rapidly deadenylate the transcript [77,116,119,120].

No-go Decay

No-go decay (NGD) is a mechanism that recognizes mRNA transcripts stalled during translation [121–123] due to damaged RNA, stress [124], or strong secondary structure that blocks the progress of translation machinery [121]. NGD is the most recently discovered RNA surveillance pathway, and as such little is known about its mechanism. However, evidence suggests that NGD may degrade mRNA in a manner that resembles translation termination. Two proteins that promote NGD, Hbs1 and Dom34, strongly resemble eRF1 and eRF3, two factors that catalyze the end of translation [121,125].

Analogous to Ski7 in NSD, Hbs1 possesses the same C-terminal domain that allows EF1a, eRF3, and Ski7 to bind the empty A site on the stalled ribosome [126,127]. Dom34 is homologous to eRF1 and binds directly to Hbs1 [126,128]. Upon binding, the Dom34/Hbs1 complex triggers the release of the nascent peptide and the ribosome is released or degraded. Likewise, the mRNA transcript is targeted for endonucleolytic cleavage and the fragments are subsequently degraded via the exosome or exonucleases [121,125]. It is not currently known how the Dom34/Hbs1 complex releases the mRNA from the ribosome, but the close relation between Hbs1 and Ski7 suggests that ribosome release may occur in the same manner as NSD. Moreover, NGD can occur independently of the Dom34/Hbs1 complex; further work is needed to identify the other factors involved.

Additionally, it remains unclear why some transcripts are targeted by NGD and not others. Pausing during translation is a normal occurrence [129] and may even serve biological functions [130–132], but only a fraction of transcripts are NGD substrates. Potentially important factors include the degree of ribosome stalling and whether or not the A site is empty to allow Dom34/Hbs1 complex binding. Further studies are needed to clarify this mechanism.

Adenylate-Uridylate-Rich Elements

While some mRNA decay pathways target faulty transcripts, others allow the cell to rapidly modulate gene expression in response to intracellular and extracellular stimuli. Several of these pathways regulate transcript levels via binding sites within the 3' UTR, including adenylate-uridylylate-rich elements (AREs), Staufen-mediated decay, microRNAs, and constitutive decay elements.

AREs are 50–150 nucleotide regions with frequent adenine and uridine bases that generally target the mRNA for rapid degradation [133,134]. The mechanism underlying this pathway is not well understood, but several RNA-binding proteins interact with these sites and modulate transcript stability. For example, overexpression of hnRNP D, also known as ARE RNA binding protein 1 (AUF1), destabilizes mRNA containing AREs [135,136]. Conversely, AUF1 depletion increases both ARE-containing mRNA stability and abundance

of the corresponding proteins [137,138]. Similarly, ablation of tristetraprolin (TTP), an RNA-binding protein that also recognizes AREs, increases mRNA and protein levels in a variety of cell types [139–141] and transcripts [142–147].

Though the exact mechanism is unclear, the association of ARE-binding proteins to AREs is followed by deadenylation [148–151], decapping, and 3' to 5' degradation via the exosome [152]. Certain subunits of the exosome bind to AREs directly, and several ARE-binding proteins including TTP associate with the exosome in vitro [75,153], ensuring rapid and preferential elimination of ARE-containing transcripts. Many ARE-binding proteins are also associated with SGs and P-bodies (discussed later in this chapter), suggesting that 5' to 3' exonuclease-mediated degradation may contribute to the turnover of ARE-containing transcripts as well [154,155]. However, not all ARE-binding proteins trigger mRNA decay. For example, the Hu family of proteins stabilize bound ARE-containing transcripts [156–159], suggesting that the effect of AREs on RNA stability depends on a combination of factors, including the ARE-binding protein, transcript, and environment.

Staufen-mediated Decay

Staufen-mediated decay (SMD) also regulates transcript levels via the 3' UTR. SMD is triggered when Stau1 recognizes double stranded RNA structures that form sufficiently downstream of the termination codon [160,161]. Stau1 binding sites (SBS) are created by intramolecular hairpin loop formation within the 3' UTR [161], or intermolecular base-pairing of the 3' UTR with partially complementary long noncoding RNA [162]. Upon binding to the SBS, Stau1 recruits UPF1, which in turn stimulates mRNA decay [160], likely in much the same way as in NMD. Moreover, given that UPF1 is critical for both SMD and NMD, there may be competition between the two pathways based on the availability of UPF1 [163].

microRNAs

microRNAs (miRNAs) are small, non-coding RNAs that base-pair with complementary sequences within RNA transcripts to trigger their decay and/or translational repression. These 20–25 nt RNAs are produced from an RNA precursor (pri-miRNA) that forms a hairpin loop shortly after transcription [164,165]. This structure is recognized by the nuclear protein DGCR8, which recruits the enzyme Drosha to cleave the hairpin from the rest of the transcript [166,167]. The resulting molecule (pre-miRNA) is then exported to the cytoplasm [168] where the enzyme DICER cuts away the looped end [169], leaving a duplex of two short, complementary RNA strands behind. Though either strand can function as a mature miRNA, one is usually degraded [170,171]. The remaining miRNA associates with the RNA-induced silencing complex (RISC), which assists in orienting the miRNA with its mRNA target, repressing translation of the target transcript and triggering its degradation.

The bound miRNA guides RISC to its binding site (miRNA recognition element or MRE) on the target transcript, most often within the 3' UTR, though binding can occur within coding regions as well [172,173]. The degree of miRNA-mRNA complementarity is a major predictor of transcript fate [174]. High degrees of sequence complementarity allow the

Argonaute family of proteins—components of RISC [175]—to catalyze RNA decay through an unknown mechanism that may involve deadenylation, decapping, or exonucleolytic degradation [176,177]. In contrast, miRNAs that bind weakly or with less complementarity induce translational repression [174] through a mechanism that remains unclear.

Constitutive Decay Elements

In addition to AREs, SBSs, and MREs, structured RNA degradation motifs may directly lead to transcript turnover. Constitutive decay elements (CDEs) are stem loop structures located within the 3' UTR that trigger mRNA decay [178,179] through recruitment of the RNA-binding protein Roquin1 [179,180]. Roquin1 binds to the CDE stem loop structure via two binding sites in its ROQ domain [180], triggering degradation by recruiting the Ccr4-Caf1-Not deadenylation complex [179]. A transcriptome-wide search of 3' UTRs in mice revealed several unique CDEs that are frequent and highly conserved across vertebrate species. Many, but not all, of these CDEs are Roquin1-associated [179], indicative of potential novel and unexplored pathways responsible for RNA decay.

Histone mRNAs

Much like CDE-containing transcripts, histone mRNAs encode highly conserved stem loop structures within their 3' UTRs. These hairpins are essential for the rapid synthesis and degradation of histone mRNA during the S phase of the cell cycle, during which the cell undergoes DNA replication and chromosome remodeling [181]. At the end of S phase, histone hairpin loops are recognized by stem loop binding protein (SLBP), which recruits the proteins necessary to add a short, oligonucleotide tail to histone mRNAs [182]. The oligonucleotide tail forms a binding site for LSM1–7, which triggers degradation via the exosome and endonucleases [182]. Interestingly, histone mRNA decay also requires UPF1 and its interaction with SLBP [183], though the exact role of UPF1 in histone mRNA metabolism remains unclear.

Processing Bodies

Processing bodies (P-bodies) are dynamic cytoplasmic foci comprised of mRNA and RNA-binding proteins. While SGs primarily sequester and protect mRNA until it can resume translation, P-bodies target associated transcripts for translational repression, decapping, and decay. Although P-body assembly is not required for RNA decay [184], it may directly compete with translation initiation; only transcripts that are not engaged in translation can be recruited to P-bodies [185–187], and upon translational inhibition P-bodies increase in number [185,188]. Conversely, a decrease in P-body components leads to an increase in mRNAs associated with actively-translating polysomes [189]. P-bodies lack translation initiation machinery [185,187], and are instead primarily composed of proteins associated with translational repression and mRNA decay, including decapping enzymes, exonucleases and NMD components [190]. This suggests that functional transcripts undergo active translation before they are recruited to P-bodies. Once transferred, the mRNA is no longer translated [189,191] and is instead degraded by decapping enzymes [192,193] or other nucleases. However, mRNAs may also escape P-bodies and resume translation [187,194],

and regulated expression of proteins such as NoBody and MLN51 can drive P-body disassembly [195,196]. Together, these observations indicate that P-bodies are part of a highly dynamic process characterized by constant flux between pools of mRNA transcripts that are being actively translated, those that are stalled or sequestered in SGs, and those that are being degraded within P-bodies.

RNA Turnover in Neurodegenerative Disease

The regulation of RNA is critical to cell health, and increasing evidence indicates that disruption of RNA stability may underlie neurodegenerative disease. Alterations in RNA turnover have been identified in several pathways, including RNA sequestration in stress granules or foci, RNA transport, the exosome, alternative splicing, and retrotransposons (Fig. 2).

RNA Sequestration

During times of stress, the cell diverts its energy and resources towards survival and recovery. A powerful mechanism to conserve resources is the sequestration of mRNAs in SGs to limit the translation of nonessential proteins. Typically, when the stressor passes, SGs dissolve and stalled mRNAs are released for translation. However, during prolonged periods of stress or disease, SGs sometimes fail to disassemble. This extended sequestration of mRNAs could effectively disrupt the delicate balance between SGs, polysomes, and P-bodies, effectively interrupting mRNA homeostasis, interfering with protein synthesis and potentially contributing to downstream toxicity in neurodegenerative diseases.

Disruption of Stress Granule Dynamics

Of the ~125 proteins identified as components of human SGs, 60% are RNA-binding proteins [197]. This group of proteins is also highly enriched for the low complexity domains that facilitate the reversible aggregation of proteins into membraneless organelles such as SGs. The mutation or mislocalization of several RNA-binding proteins stabilize SGs, sometimes driving them to form irreversible aggregates that sequester mRNA and RNA-binding proteins indefinitely and disrupt SG homeostasis. Conversely, though the machinery that drives SG disassembly remains unclear, any errors within this pathway may likewise lead to RNA dyshomeostasis and subsequent disease.

RNA-binding Proteins in Stress Granule Dynamics

TDP43 and FUS are two stress granule components that are integrally involved in neurodegenerative disease, particularly amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Both TDP43 and FUS are primarily nuclear proteins, but their cytoplasmic mislocalization [198–200] and nuclear exclusion [201–203] are characteristic features of ALS and FTD. These proteins are capable of nucleocytoplasmic shuttling: in response to various stressors they associate with cytoplasmic SGs, but when the stress has passed they return to the nucleus [204]. ALS-linked mutations in the genes encoding TDP43 and FUS promote increased association with SGs [202,205], abnormal SG formation [206], and reduced SG dissociation [207,208]. TDP43 and FUS play important

roles in alternative splicing and the stress response, and their sequestration impacts the processing of several transcripts that are critical for neuronal viability [209,210]. Likewise, excess cytoplasmic TDP43 and FUS may sequester related RNA-binding proteins within SGs, further disrupting RNA homeostasis [64]. Importantly, TDP43- and FUS-related toxicity relies upon the ability of these proteins to bind RNA. Deletion of the RNA recognition motifs in either protein greatly reduces toxicity without affecting localization [211,212], suggesting that RNA binding, not localization, imparts toxicity. Furthermore, these observations indicate that the sequestration of mRNAs themselves, not just RNA-binding proteins, is particularly damaging to neurons.

ALS-linked mutations are also found in other RNA-binding proteins such as Matrin3 [213], hnRNPA1, hnRNPA2/B1 [214], and TIA1 [215], all of which associate with SGs. These mutations are often centralized within the proteins' low complexity domains, and evidence indicates that they likewise alter SG dynamics, suggesting a link between SG association/dissociation and pathogenicity.

Stress Granule Disassembly

Though relatively little is known about SG disassembly, evidence suggests that valosin-containing protein (VCP) is crucial for this phenomenon. VCP regulates several cellular processes including autophagy [216], chromatin remodeling [217], and membrane trafficking [216], as well as SG clearance [218]. VCP accumulates in SGs, and its knockdown results in the persistence of SGs even after the stressor has passed [218]. Moreover, mutations in the gene encoding VCP cause a multisystem proteinopathy that includes ALS and FTD [219], and the overexpression of mutant VCP results in impaired SG disassembly [218]. Thus, pathogenic mutations in the genes encoding VCP, TDP43, and FUS all stabilize SGs, thereby effectively sequestering essential mRNA and RNA-binding proteins within these organelles. A such, altered SG dynamics and abnormal RNA stability may represent a conserved pathway underlying ALS, FTD and related neurodegenerative diseases.

Nucleotide Repeats and RNA Foci

Microsatellites are repeated tracts of nucleic acids that compose approximately 50% of the human genome [220]. These regions are a source of genomic instability, and expansion mutations that increase the number of repeats above a certain threshold can lead to neurodegenerative diseases such as Huntington's disease (HD), myotonic dystrophy (DM), spinocerebellar ataxias, Freidrich's ataxia, fragile X syndrome, fragile X-associated tremor ataxia syndrome (FXTAS), ALS and FTD [221,222]. In most cases, the length of the expanded region is inversely correlated with prognosis — higher repeat number results in earlier onset and more severe symptoms. Repeat expansions have unique pathological implications— they form unique secondary structures that may disrupt translation, sequester RNAs and other proteins into nuclear foci, and serve as a substrate for non-canonical translation.

Repeat Expansion Secondary Structure

The majority of expansion mutations associated with disease are trinucleotide CNG repeats, where N is any nucleotide. Due to the high degree of complementarity, CCG, CAG, CUG, and CGG repeats readily form mismatched hairpin loops [223] whose stability increase proportionally with the number of repeats [224]. Tetra-, penta-, and hexa-nucleotide repeats also form hairpins [225], though they appear to be less stable.

Repeat expansions with a high percentage of guanine nucleotides can also form G-quadruplexes. In these structures, four guanine bases associate through Hoogsteen hydrogen bonding to form a square guanine tetrad, and two or more tetrads stack to form a G-quadruplex [226]. Whether or not G-quadruplexes exhibit a physiological function remains unknown, but some evidence indicates that they participate in transcriptional regulation and/or telomere maintenance [227]. They are also observed in association with cancer, copy number variants, and age-related disease, specifically ALS and FTD. The most common mutation responsible for inherited ALS and FTD consists of a GGGGCC (G4C2) repeat expansion in the first intron of C9orf72 [228,229]. Unaffected individuals have 2–8 (G4C2) repeats [230], but tracts of > 32 (G4C2) repeats lead to ALS, FTD, or both with nearly 100% penetrance by age 80 [231]. These repeats form stable G-quadruplexes [232], which are further stabilized in longer repeat expansions [233].

(G4C2) repeat expansions also form structures known as R-loops at the site of transcription, composed of nascently-synthesized RNA hybridized to the complementary DNA strand [234,235]. The unbound DNA strand may also form hairpins or G-quadruplexes, further stabilizing the loop [236]. In addition to C9orf72-related ALS/FTD, R-loops are also observed in fragile X syndrome and Friedreich's ataxia [237] characterized by CGG and GAA trinucleotide repeats, respectively. The abundance of R-loops in these disorders depends on the size of the repeat expansion, with higher repeat number correlating with more frequent R-loops. These structures may contribute to the pathology of expansion diseases in several ways: by blocking translation [238], disrupting chromatin remodeling [239], or promoting genomic instability at the repeat expansion site [235]. In support of the pathogenic effects of R-loops, mutations in the gene encoding senataxin (SETX), a helicase that helps resolve R-loops [240], cause juvenile ALS (ALS4), while SETX overexpression prevents neurodegeneration in ALS models [241].

RNA Foci

In addition to their effects on RNA stability and translation, the propensity of repeat expansions to form stable secondary structures contributes to the formation of RNA foci [242,243]. These nuclear inclusions may drive pathogenesis through the sequestration and nuclear retention of specific RNA-binding proteins. For example, CUG repeat expansions in DMPK cause myotonic dystrophy type 1 (DM1), a neuromuscular disease characterized by progressive muscle loss and weakness. This repeat expansion sequesters and disrupts the splicing activity of muscleblind (MBNL) [244,245], a protein responsible for the processing of several key downstream transcripts [246]. MBNL binds to hairpins that result from repeat expansion mutations in DMPK with high affinity [245,247], and preventing MBNL

sequestration via small molecules that recognize CUG hairpin loops restores its splicing activity and helps maintain RNA homeostasis in DM1 models [248]. Additionally, the RNA foci observed in DM1 [249] and myotonic dystrophy type 2 (DM2) [250] sequester several other RNA-binding proteins, suggesting that global disruption of alternative splicing may contribute to DM pathogenesis [251]. RNA foci are also observed in C9orf72-linked ALS/FTD [252], where the G4C2 repeat transcripts sequester several splicing factors including hnRNPA1, hnRNPH, and SC35, as well as the RNA-binding protein hnRNPA3 and the mRNA export receptor ALYREF [253]. The sequestration of proteins essential to multiple cellular processes by repeat expansion transcripts suggests that these diseases occur, at least in part, through an RNA gain of function mechanism.

Repeat Associated Non-AUG (RAN) Translation

Nucleotide repeats can be translated into polypeptides even if they are not located within a traditional open reading frame, via a non-canonical pathway termed repeat associated non-AUG (RAN) translation. RAN translation may be triggered by hairpin loops formed by repeat-containing stretches of DNA, which effectively stall ribosome scanning and facilitate translational initiation at near-AUG codons [254–256]. This process occurs in multiple reading frames in both the sense and antisense directions, producing several dipeptide repeat-containing proteins (DPRs) [254]. RAN translation products are detected in spinocerebellar ataxia type 8, HD [257], DM1 [254], FXTAS [256], and C9orf72-associated ALS/FTD [258], suggesting that RAN translation is a common phenomenon in repeat expansion diseases. In some cases, there appears to be an inverse relationship between RAN translation and RNA foci formed by repeat expansions. This observation suggests that the repeat-expanded RNA may be sequestered in nuclear foci, precluding nuclear export and subsequent translation [259]. This may serve as a coping response to prevent the translation of DPRs; failure of this coping response over time may result in increased RAN translation and subsequent neurodegeneration [260,261]. In support of this hypothesis, RNA foci in C9orf72 mutant mice are abundant yet rarely associated with neurodegeneration [261]. RAN peptides may also affect RNA stability by disrupting membraneless organelles such as the nucleoli [262] and Cajal body [263], which are responsible for ribosomal RNA [264] and spliceosome maturation [265], respectively. Lastly, an increase in SGs and a decrease in P-bodies is observed in neurons expressing RAN peptides [266]; in this case, RAN peptides may act similarly to small proteins such as NoBody [195] that dissolve P-bodies, releasing unstable RNAs to be sequestered by SGs. Additional studies are required to determine the effect of RAN peptides on RNA stability, P-body dynamics, and global RNA homeostasis.

RNA Transport

The diverse functions of RNA are determined, in part, by its subcellular localization. As a result, RNA transport mechanisms are crucial for RNA function, particularly in highly compartmentalized and morphologically complex cells such as neurons. Among the most important of these mechanisms is nucleocytoplasmic transport, in which RNA transcripts are shuttled from the nucleus to the cytoplasm. Several neurodegenerative diseases exhibit deficits in nucleocytoplasmic RNA transport, leading to RNA sequestration in the nucleus

and widespread dysregulation of gene expression. Thus, interruption of nuclear export machinery can have severe consequences on neuronal health.

Impaired Nuclear Export

Nuclear mRNA export is triggered by deposition of the highly conserved translation export (TREX) complex at the 5' end of the nascent transcript [267]. The core of this complex, THO, recruits ALYREF and several other nuclear export factors [268–271]. ALYREF then binds to nuclear export factor 1 (NXF1) [272], triggering a shift from a conformation with low RNA binding affinity to one that readily binds the transcript [273,274]. NXF1 directs the transcript to the nuclear pore complex (NPC), a large multimeric structure that spans the nuclear envelope and enables the transport of molecules into and out of the nucleus. NXF1 facilitates NPC docking and transcript translocation via interactions with NPC components containing low complexity domains enriched in phenylalanine and glycine residues [275].

Disruption of this pathway leads to nuclear retention of RNA, and which is then rapidly degraded by the nuclear exosome [276,277]. Interrupting nuclear RNA export can have severe consequences for neuronal survival, and mutations in nuclear export components are linked to several neurological and neurodevelopmental disorders. Chromosomal translocation and inactivation of THOC2, a subunit of the core TREX complex, leads to cognitive impairment, cerebellar hypoplasia, and congenital ataxia in humans [278]. Additionally, missense mutations in THOC2 have been implicated in fragile X syndrome [279], and mutations in a second THO subunit, THOC6, lead to intellectual disabilities [280]. Moreover, loss of function mutations in Gle1 results in ALS [281] and fetal motor neuron disease [282]. Gle1 is a nuclear export mediator located on the cytoplasmic face of the nuclear pore that facilitates both the release of the transcript from the nuclear pore and its dissociation from export adaptor proteins [283], freeing it to undergo translation. This process may be specific to mRNAs with poly(A) tails, as depletion of Gle1 results in a nuclear accumulation and subsequent degradation of polyadenylated mRNAs [284,285].

Abnormal nucleocytoplasmic transport is also a characteristic finding in models of ALS [286–288], DM1 [289] and HD [290,291]. Toxicity in these models can be suppressed by pharmacologic or genetic modulation of nuclear transport components, testifying to the broad significance of this pathway in disease pathogenesis. Moreover, age is a likely contributor to impaired nuclear import, as aged cells display abnormal NPCs and reduced expression of nucleocytoplasmic transport genes [292,293]; the resulting reduced fidelity in nuclear import/export is consistent with the observed age-dependent risk of nearly every neurodegenerative disease.

Disruption of the Nuclear Pore

In addition to disruption of the recruitment of the transcript to the pore, interruption of the pore itself can alter nucleocytoplasmic transport. RAN translation of repeat expansion mutations produces several DPRs. Some of these DPRs, including arginine-rich dipeptides generated from RAN translation of the C9orf72 G4C2 repeat in familial ALS/FTD, clog the nuclear pore and inhibit the transport of RNA and other macromolecules into and out of the

nucleus [294]. Again, this contributes to the nuclear retention of RNAs that are susceptible to exosome-mediated decay [276,277]. Arginine-containing DPRs are among the most toxic of the dipeptides in ALS/FTD models [262,295], suggesting that impaired nucleocytoplasmic transport contributes significantly to neurodegeneration in these disorders.

The RNA Exosome Complex

The exosome complex is an RNA degradation mechanism that contributes broadly to RNA turnover, surveillance, and processing. This complex works closely with other pathways to orchestrate the degradation of immature, abnormal, or misplaced RNA.

Exosome-Associated Mutations in Neurodegenerative Disease

Due to the importance of the exosome in regulating RNA decay, mutations in this complex can have severe implications. Mutations in EXOSC3, the gene encoding the core exosome component RRP40, are linked to autosomal recessive pontocerebellar hypoplasia type 1 (PCH1) [296]. This progressive neurodegenerative disease is characterized by atrophy of the pons and cerebellum and loss of spinal motor neurons, accompanied by developmental delay, muscle atrophy, and difficulty breathing [297]. 37% of PCH1 patients exhibit EXOSC3 mutations, most of which are heterozygous missense mutations [297]. Disease severity correlates with genotype, as patients with homozygous missense mutation fare better and those with a combined missense and null mutation fare worse [298].

Similarly, mutations in a gene encoding a separate exosome component, EXOSC8, result in cerebellar hypoplasia (CH) [299]. This autosomal recessive disorder is also characterized by progressive degeneration of the cerebellum, pons, and spinal motor neurons, as well as abnormal myelination. Though the mechanism is unclear, an increase in exosome substrates, including ARE-containing mRNAs encoding myelin proteins, in CH models suggests that impaired exosome function may contribute to dysmyelination of the involved tracts and subsequent neurodegeneration [299].

Alternative Splicing

Between 92 and 94% of all genes in the human genome are alternatively spliced [300], and the brain expresses more alternatively spliced genes than any other organ [301,302]. This suggests that alternative splicing is a key regulator of transcript stability and gene expression, and its misregulation can have severe effects on neuronal health [303].

Nonsense-Mediated Decay and Unannotated or “Cryptic” Exon Splicing

A primary consequence of alternative splicing is RNA destabilization [101]. As discussed above, in many cases alternative splicing may serve to regulate normal transcript levels. This is supported by the fact that over one third of RNA transcripts are spliced to include PTCs, and these transcripts are likely targeted for degradation via NMD [101]. Mutations that affect splicing and result in either the inclusion of PTC-encoding exons or a shift the reading frame that uncovers ‘silent’ PTCs may destabilize transcripts and lead to disease via gene

haploinsufficiency. For example, disease-associated missense GRN mutations cause ALS and FTD by altering mRNA splicing, triggering NMD of GRN transcripts, and consequent reductions in progranulin protein expression [304–307]. In other cases, mutations that create novel splice sites or the dysregulation of splicing factors leads to the inclusion of unannotated or “cryptic” exons and the production of faulty transcripts that are eventually targeted for decay. Several regulatory proteins suppress these unannotated exon splicing events, including TDP43. Depletion of TDP43 results in a widespread increase in cryptic exon splicing events, and the inclusion of these exons may lead to NMD [308,309]. Many of these events are specific to neurons [310], which suggests that the disruption of TDP43-mediated cryptic exon regulation may contribute to ALS and FTD.

NMD can be manipulated through the modulation of specific pathway components: overexpression of UPF1 and UPF3B stimulate NMD, while UPF1 knockdown or the overexpression of UPF3A, an antagonistic paralog of UPF3B that sequesters UPF2, suppress NMD [311]. Consistent with a potential link between NMD and ALS/FTD pathogenesis, overexpression of UPF1 or UPF2 prevents FUS- and TDP43-mediated neurodegeneration in model systems [312]. One possibility is that UPF1 overexpression in these models prevents cell death by boosting endogenous NMD, thereby enabling the pathway to properly metabolize an overabundance of NMD substrates. However, further investigation is required to confirm and extend these findings.

Retrotransposons

Transposable elements (TEs) are mobile genetic elements that constitute a large portion of most eukaryotic genomes. Retrotransposons, which encode a reverse transcriptase and an integrase that allow them to “copy and paste” themselves from one region to another, represent approximately 40% of the human genome [313]. Though the vast majority of retrotransposons are inactive [314], some retain the ability to mobilize. Retrotransposition occurs approximately once every 10–100 births [315], and the insertion of these elements near or within active genes is a significant source of genomic instability and cellular toxicity [316,317]. Though transcription of these regions is downregulated [318,319], the transcripts that are transcribed are degraded via NMD [320] and other non-canonical pathways [321]. Several mechanisms have also evolved to suppress retrotransposon expression and prevent the resultant large scale deletions and genomic rearrangements [322], and the efficiency of these mechanisms declines with age [316,323,324]. Moreover, the elevated expression of retrotransposons correlates with several neurodegenerative disorders [325–327], suggesting that a reduction in retrotransposon repression may contribute to disease pathogenesis.

Retrotransposons in ALS

As previously discussed, TDP43 aggregation and mislocalization play a fundamental role in ALS and FTD, and TDP43 serves as a key regulator of alternative splicing for hundreds of transcripts. TDP43 also recognizes several TE-derived RNA transcripts [328], and this binding is reduced in FTD patients coincident with elevated TE expression. This suggests that TDP43 normally regulates TE expression, and the loss of functional TDP43 in FTD results in TE overexpression [328]. This is further supported by the finding that TEs are

derepressed in ALS/FTD models involving TDP43 overexpression or knockdown [328,329], suggesting that TE dysregulation may contribute to neurodegeneration in ALS and FTD. This may occur through activation of DNA damage-mediated programmed cell death due to the large scale deletions and genomic rearrangements that result from de-repressed TEs [329], and there is some evidence to suggest that TDP43 pathology impairs siRNA-mediated gene silencing, an essential system that normally protects the genome from retrotransposons [329]

Human endogenous retroviruses (HERVs) represent a subclass of retrotransposons originating from ancient viral infections that resulted in the integration of viral DNA into the host genome. The most recent of the retroviruses to integrate into the human genome is HERV-K [330]. The HERV-K envelope protein is expressed in both cortical and spinal neurons of ALS patients, suggesting activation of the retrovirus in disease. Furthermore, ectopic expression of the HERV-K envelope protein triggers neurodegeneration and motor dysfunction in mice [331]. Like other retrotransposons, HERV-K is regulated by TDP43, suggesting that HERV-K derepression in TDP43-deficient cells might contribute to neurodegeneration in ALS [331].

Retrotransposons in Aging

Age is a major risk factor for most neurodegenerative diseases, likely due to a reduced ability regulate protein degradation [332], oxidative stress [333], and DNA damage [334]. While retrotransposons are a significant source of genomic instability, additional evidence suggests that they are more destructive in aging brains. The expression and mobility of several TEs increase with advanced age [316,324]; these changes, in turn, are linked to progressive, age-dependent memory impairment and shortened lifespan [324]. Thus, the derepression of retrotransposons during normal aging could contribute to the age-related increase in risk for neurodegenerative diseases.

Conclusions and Future Directions

Neurodegenerative diseases vary widely in clinical presentation, neuropathology, and genetic background. However, it is becoming increasingly clear that alterations in RNA turnover are a key contributor to disease pathogenesis. The magnitude and extent of RNA dyshomeostasis observed in neurodegenerative disease models strongly suggests a fundamental disruption of one or more of the many mechanisms that tightly regulate RNA stability. While compensatory pathways may allow cells to cope with subtle changes in SG dynamics, alternative RNA splicing or RNA degradation, over time such pathways become less efficient and the ability of the cell to maintain RNA homeostasis slowly erodes. Mitotic cells evade toxicity by dilution and division, but for long-lived cells such as neurons, the resulting abnormalities eventually lead to cell death. Because altered RNA stability results from the disruption of several related but distinct pathways, it is unlikely that focusing on single transcripts will result in a cure. Instead, a more complete understanding of RNA degradation in both healthy and diseased conditions may highlight common mechanisms and key upstream elements that could be rationally targeted for therapeutic development.

Abbreviations

RNA	ribonucleic acid
mRNA	messenger RNA
ncRNA	non-coding RNA
CPSF	cleavage/polyadenylation specificity factor
PAB2	polyadenylate binding protein 2
UTR	untranslated region
CBC	cap binding complex
tRNA	transfer RNA
SG	stress granule
PTC	premature stop codons
NMD	nonsense-mediated decay
EEJ	exon exon junction
EJC	exon junction complex
SURF	surveillance complex
RUST	regulated unproductive splicing and translation
uORF	upstream open reading frame
NSD	nonstop-mediated decay
NGD	no-go decay
ARE	adenylate-uridylate-rich element
AUF1	ARE RNA binding protein 1
TTP	tristetraprolin
SMD	staufen-mediated decay
Stau1	Staufen-1
SBS	staufen binding site
miRNAs	microRNAs
RISC	RNA-induced silencing complex
MRE	miRNA recognition element
CDE	constitutive decay element

SLBP	stem loop binding protein
P-bodies	processing bodies
ALS	amyotrophic lateral sclerosis
FTD	frontotemporal dementia
VCP	valosin-containing protein
HD	Huntington's disease
DM	myotonic dystrophy
FXTAS	fragile X-associated tremor ataxia syndrome
ALS4	Juvenile ALS
DM1	myotonic dystrophy type 1
MBNL	muscleblind
DM2	myotonic dystrophy type 2
RAN translation	repeat associated non-AUG translation
DPR	dipeptide repeat
TREX complex	translation export complex
NXF1	nuclear export factor 1
NPC	nuclear pore complex
PCH1	pontocerebellar hypoplasia type 1
CH	cerebellar hypoplasia
TE	transposable element
HERV	human endogenous retroviruses

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Figure 1.

Pathways responsible for RNA homeostasis. RNA stability is promoted by two key mechanisms (left). Following transcription, nascent RNA is stabilized by the addition of a 5' cap and poly(A) tail, as well as the formation of secondary structures. Transcripts are also sequestered and stabilized in stress granules upon exposure to cellular stress. In contrast, RNA degradation pathways target faulty transcripts for removal (right). Transcripts that contain premature stop codons are targeted by nonsense-mediated decay. When translation fails to stop or start, the associated transcripts are degraded by nonstop decay and no-go decay, respectively. RNA decay mechanisms also regulate transcript abundance through several elements located within the 3' UTR, including AU-rich elements, Staufen binding sites, miRNA recognition elements, and constitutive decay elements. Lastly, P-bodies sequester and destabilize RNA transcripts.

Figure 2.

Abnormal RNA stability in neurodegenerative disease. Here we compare how normal pathways (left column) are disrupted in disease (right column). **RNA Sequestration:** There is constant flux between pools of RNA transcripts that are actively being translated (the polysome), those sequestered in stress granules, and those associated with P-bodies. In disease states, increased stress granule formation or reduced stress granule dissociation disrupts the equilibrium, resulting in fewer transcripts undergoing translation. **Repeat Expansions and RNA Foci:** Transcripts containing repeat expansions form secondary structures such as hairpin loops and G-quadruplexes that are often stabilized in nuclear foci, which also sequester RNA-binding proteins (green circles). These transcripts also generate proteins via RAN translation that can disrupt membraneless organelles involved in RNA splicing and processing. **RNA Transport and the Exosome:** Mutations in THO, Gle1, and other components of the RNA export pathway result in nuclear RNA retention and degradation via the exosome complex. Mutations in exosome components can inhibit RNA turnover and further disrupt RNA homeostasis. **Alternative Splicing:** Mutations that disrupt splice sites, or dysfunction of splicing regulators such as TDP43, result in the inclusion of unannotated or “cryptic” exons (pink). These transcripts are often targeted for nonsense-mediated decay. **Retrotransposons:** These transposable elements insert themselves into the

genome, often disrupting open reading frames or splice sites. The transcripts that are transcribed from these regions are often faulty, and are targeted for RNA decay.

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