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The role of Matrin-3 in physiology and its dysregulation in disease

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Abstract

The dysfunction of a number of RNA-binding proteins that are heavily disordered, including TDP-43 and FUS, are implicated in amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD). These proteins serve a number of important roles in the cell, and their capacity to form biomolecular condensates is key to their function, but also a vulnerability that can lead to misregulation and disease. Matrin-3 (MATR3) is an intrinsically disordered RNA-binding protein implicated both genetically and pathologically in ALS/FTD, though it is relatively understudied as compared to TDP-43 and FUS. In addition to binding RNA, MATR3 also binds DNA and is implicated in many cellular processes including the DNA damage response, transcription, splicing, and cell differentiation. It is unclear if MATR3 localizes to biomolecular condensates under physiological conditions, which is brought further into question due to its lack of a prion-like domain. Here, we review recent studies regarding MATR3 and its roles in numerous physiological processes, as well as its implication in a range of diseases.

Introduction

Matrin-3 (MATR3) was originally identified in 1991 as a component of the nuclear matrix, which is thought to be a ribonucleoprotein network within the inner nucleus that forms a scaffold to promote chromatin organization (1, 2). The presence and composition of a nuclear matrix has remained somewhat controversial, due to a lack of early evidence of such a structure in cellular imaging (3, 4). Since its identification, further studies of MATR3 have delineated how its two zinc finger motifs (ZFs) and two tandem RNA recognition motifs (RRMs) interact with DNA and RNA (5–8). These investigations showed that MATR3 is involved in diverse processes involving nucleic acids including transcription, splicing, RNA stabilization, and the DNA damage response (8–11). MATR3 is highly conserved, essential during development, and ubiquitously expressed (5, 12). Expression of MATR3 is tightly regulated in a tissue-specific manner and is highest during fetal development. At maturity, MATR3 expression is highest in reproductive organs and lowest in muscle and the spinal cord, key areas that are vulnerable to dysregulation of MATR3 (12). Indeed, MATR3 mutations have been implicated in a distal myopathy, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) (13, 14).

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ALS is a lethal neurodegenerative disorder where loss of upper and lower motor neurons causes progressive muscular atrophy. FTD is characterized by degeneration of the frontal and temporal cortices which causes personality and behavioral changes. Clinical, pathological, and genetic links between ALS and FTD indicate that they coexist on a spectrum of neurodegenerative disease (15, 16). Many disordered RNA-binding proteins (RBPs) like MATR3 have been implicated in ALS/FTD, of which TDP-43 is perhaps the most heavily studied due to its high prevalence in pathological inclusions. Generally, the RBPs implicated in ALS/FTD function in a range of nucleic acid regulatory processes and contain prion-like domains which are often mutational hotspots (17). Further, the prion-like domains of these RBPs often drive their assembly in biomolecular condensates (BMCs) as a part of their normal physiology. However, increased concentrations of disordered RBPs in BMCs can drive conversion of the condensates to gel- or solid-like states, as well as aggregation of these species, potentially giving rise to their accumulation in pathological cytoplasmic inclusions, which are commonly found in ALS/FTD (15, 16). Due to the occurrence of a number of different disordered RBPs in ALS/FTD, it is thought that the disruption of RNA homeostasis and corruption of BMCs may be central to disease pathogenesis.

Similar to other ALS/FTD-associated RBPs, MATR3 is highly disordered except for its ZF and RRM domains, although it does not contain a prion-like domain (PrLD) (18). Though MATR3 lacks a PrLD, its enrichment in tyrosine and arginine suggests it may still undergo phase separation to form BMCs (19, 20). Mutations within the disordered regions of MATR3 are associated with adult-onset ALS/FTD and a distal myopathy while mutations identified within the RRMs are associated with childhood neurological disorders (13, 14, 21–23). While MATR3 mutations account for <1% of familial ALS/FTD cases, pathological inclusions of wild-type MATR3 have also been observed in sporadic ALS/FTD (24–31). Understanding the properties and dysregulation of MATR3 is crucial to unravelling the puzzle of ALS/FTD pathogenesis. Here, we review the physiological roles of MATR3 as well as its features, phase properties, and nucleic acid regulatory roles. We also examine the genetic and clinical evidence of MATR3 dysregulation in ALS/FTD and myopathy, as well as review the findings about ALS/FTD-linked MATR3 mutations.

Physiological Roles of MATR3

Features of the MATR3 sequence

MATR3 is an 847 amino acid protein comprised of a mixture of disordered regions and functional domains. It contains two tandem RRMs (RRM1 residues 398–473, RRM2 residues 496–575), two C2H2-type ZFs (ZF1 residues 288–322, ZF2 residues 798–833), and a nuclear localization sequence (NLS, residues 588–595) (Figure 1, top) (1, 5). As predicted by multiple algorithms and AlphaFold, MATR3 is almost entirely disordered outside of the nucleic acid binding domains which are predicted to adopt canonical folds (Figure 1, bottom) (18, 32–34). The disordered regions of MATR3 are not well-characterized, though MATR3 is known to lack a prion-like domain and to contain many negatively charged residues in the C-terminal disordered region, giving it acidic properties (1, 18, 34). Importantly, many of the known ALS/FTD-associated MATR3 mutations are found in these

disordered regions. Truncated isoforms of MATR3 can arise via alternative splicing and have been observed as multiple MATR3 bands in immunoblotting, however these isoforms have yet to be characterized (5, 7, 23, 35–39).

Many questions remain unanswered about the molecular features of MATR3, likely due to the challenges associated with biochemical investigations of such a large and disordered protein. The ZFs and RRMs of MATR3 likely interact with DNA, RNA, and protein and may compete with each other for binding sites (5, 23, 40–42). MATR3 is known to bind to introns (43, 44), polypyrimidine tracts (39), and noncoding enhancer regions (45). Its ZFs are known to bind adenine/thymine rich DNA sequences (5) while its RRMs are known to bind to single-stranded pyrimidine-rich RNA sequences (39, 46, 47), although it is unclear if either RRM plays a dominant role (5, 9, 44, 46). Phosphorylation of MATR3 has been shown to greatly enhance its DNA and RNA binding affinity, though the specific sites of phosphorylation have not yet been identified (8, 46). To our knowledge, the key nucleic acid binding residues of MATR3, as well as the nucleic acid sequence determinants of binding, have not yet been elucidated.

Phase Separation of MATR3

Biomolecular condensates (BMCs) such as stress granules or mRNA processing bodies provide an additional level of subcellular compartmentalization (48–50). Condensates are formed via liquid-liquid phase separation whereby biomolecules such as associative proteins and RNAs form dilute and condensed phases. Condensates typically display liquid-like properties, such as dynamic movement within the condensate and fusion of condensate droplets upon contact (48–50). Typically, BMCs readily form and dissipate in response to cellular and environmental signals, allowing reversible sequestration of cellular components. Disruption of this reversibility by mutations, stress, or aging may modulate the properties of the condensates, decreasing their dynamics and driving conversion to gel- or solid-like states. These less dynamic condensates can lead to the accumulation of misfolded protein in inclusions, and such inclusions are often associated with disease (51). Many ALS/FTD-associated RBPs, including TDP-43 and FUS, contain a prion-like domain enriched in glycine and uncharged amino acids which can drive phase separation. Indeed, TDP-43 and FUS have been shown to form condensates in vitro that, with aging, can transition from dynamic liquid states to gel- and solid-like states (52, 53). Inclusions of TDP-43 and FUS are associated with ALS/FTD pathology (51). Further, TDP-43 and FUS display punctate staining, suggesting localization to a physiological condensate (52, 54).

In contrast to TDP-43 and FUS, MATR3 does not contain a prion-like domain and generally displays nuclear granular staining, forming a layer of small assemblies with variable intensities that are distinct from the larger punctate structures typical of BMCs (1, 14, 18, 42, 45, 55–63). While TDP-43 and FUS are known components of stress granules, studies conflict on whether MATR3 localizes to sodium arsenite-induced stress granules (Figure 2) (35, 55, 64, 65). One study suggests that MATR3 binds to the lncRNA *NEAT1* in primary myoblasts and modulates paraspeckle formation (Figure 2) (66). However, these effects may be indirect, as MATR3 binding to *NEAT1* may be mediated by the RBP PABPN1 and localization of MATR3 to paraspeckle structures has not been shown (66).

Most of the evidence linking MATR3 to BMCs comes from studies where the MATR3 – RNA interaction is altered. Namely, MATR3 RRM deletion constructs form large spherical puncta with liquid-like properties (18, 33, 35, 42, 44, 63). In mouse hepatocytes, MATR3 staining shifts from a granular staining pattern to form large spherical puncta upon the addition of an RNA transcription inhibitor, which decreases the amount of RNA present (44). The N-terminal disordered region of MATR3 is sufficient to drive foci formation even in the absence of RRMs (18, 63), and truncations of MATR3 with likely disrupted RRMs localize to cytoplasmic mRNA processing bodies (Figure 2) (35). Expression of full-length *H. sapiens* MATR3 in *S. cerevisiae* resulted in the formation of multiple distinct nuclear foci rather than granular staining, possibly due to the yeast cell having fewer optimal RNA binding partners for MATR3 compared to its native environment (18). Altogether, this evidence suggests that condensation of MATR3 may be antagonized by physiological RNA binding. Although TDP-43 and FUS undergo phase separation in RNA-binding deficient states, ablated RNA binding is not required for TDP-43 or FUS to achieve phase separation (53, 67–69). It is not yet understood if the physiological nuclear granular staining of MATR3 represents localization to atypically small BMCs or a different type of MATR3 assembly altogether. If MATR3 localization to BMCs does in fact require tuning of MATR3 – RNA interactions, the factors modulating this interaction and thus driving phase separation of MATR3 remain unclear. It also remains unclear if MATR3 phase separation is physiological or pathological.

Functions of MATR3

As is common among RBPs, MATR3 has been linked to numerous processes involving nucleic acid metabolism and nuclear organization including the DNA damage response, transcription, alternative splicing, mRNA stabilization and export, nuclear retention of A-to-I hyperedited RNA, and RNA silencing and degradation (Figure 2) (reviewed in (23, 34, 70)). Additionally, MATR3 has recently been shown to repress cryptic exon inclusions (22). It is unclear whether direct interaction of MATR3 with nucleic acids or indirect interactions of MATR3 with other machinery drives these processes. Notably, MATR3 has been shown to interact with many RNA processing proteins including TDP-43 and FUS, although it is unclear if these interactions are nucleic acid dependent (34, 70–72).

MATR3 likely plays a role in nuclear organization, as it was originally identified as a component of the putative inner nuclear matrix (1). The nuclear matrix is proposed to be a ribonucleoprotein network that provides scaffolding for chromatin organization, although the presence of a nuclear matrix remains controversial because visualization of this network has been elusive (3, 4, 73, 74). Recently, Zhang et al. visualized a fibrous mesh-like nuclear network of MATR3 and antisense *LINE-1* lncRNA (AS-L1) using super-resolution microscopy in mouse hepatocytes, which the authors suggest provides evidence supporting the existence of a nuclear matrix (44). Knockdown of MATR3 or AS-L1 in this system resulted in chromatin reorganization as well as a shift from granular to punctate staining of MATR3 (44). Additionally, MATR3 has been observed to interact with chromatin organization machinery and the nuclear envelope, supporting the idea that MATR3 is implicated in nuclear organization (8, 59, 75–77). MATR3 also interacts with long noncoding RNA X-inactive specific transcript (*Xist*) and the RBPs TDP-43, CELF,

and PTBP1 to form a condensate which initiates inactivation of the X chromosome (78, 79). Maintenance of the inactivated X chromosome does not depend on *Xist*, but rather the RBP complex in addition to epigenetic modifications such as DNA methylation (78, 80). Although these findings suggest that MATR3 is important for nuclear organization, further investigations are required to understand the mechanism driving MATR3 network formation, which MATR3 functions depend on network formation, and how chromatin organization may be disrupted by MATR3 dysregulation or mutation in disease.

Despite the possible role of MATR3 in nuclear organization, altered expression of MATR3 does not broadly alter global gene expression (39, 41, 42). However, several studies have shown that MATR3 is important for cell differentiation (44, 76, 81–83). Spatial and temporal chromatin reorganization is critical for altering gene expression as needed during development and cell differentiation. Decreased MATR3 expression results in chromatin reorganization, thereby accelerating cell differentiation by modulating interactions that mediate chromatin organization (44, 76, 84). MATR3 expression also maintains the undifferentiated pluripotent state of induced or neural stem cells and may regulate transcriptome-wide changes driving hippocampal neurogenesis (82, 83, 85). Further MATR3 regulates dendritic spine morphogenesis in hippocampal neurons through its processing of microRNA precursors (86). MATR3 is essential for muscle and heart cell differentiation where it interacts with lncRNA to coordinate chromatin reorganization for myogenic transcription programs, likely through phase separation (59, 66, 81). Supporting this link, a congenital heart defect was reported in a case of MATR3 chromosomal translocation that resulted in upregulated MATR3 expression (87). Further, it has been observed that higher levels of MATR3 expression are maintained during development as compared to maturity (12, 87, 88). The importance of MATR3 during development is further supported by the deleterious impacts on viability due to MATR3 knockdown in several model systems (82, 87, 89). The role of MATR3 in cell differentiation and chromatin organization suggests that these important processes may be mediated through the formation of a nuclear network of MATR3 which scaffolds chromatin.

MATR3 in Disease

MATR3 Mutations and Pathology

Sixteen MATR3 mutations have been identified in patients largely through exome sequencing (Figure 1, Table 1) (14, 21, 22, 25, 26, 28–30, 90–92). While MATR3 was linked to a family with distal myopathy in 1998, it was not until 2009 that the autosomal dominant point mutation S85C was identified (13, 93). In 2014, exome sequencing of familial ALS cases identified mutations within the disordered regions of MATR3 (14). Significantly, the S85C mutation was identified in ALS cases as well as myopathy, though some myopathy cases were later reclassified as slowly progressing ALS (14). Patients harboring the S707L mutation in MATR3 displayed cognitive defects determined to be FTD, linking MATR3 to dementia (27). Though initially the MATR3 F115C mutation was associated with ALS, more recently, the identification of an additional mutated protein, KIF5A, in this patient suggests that F115C should be reclassified as nonpathogenic (94). Additionally, the MATR3 RRM point mutations E436K and M548T were identified in

singular cases of severe childhood neurological disorders (21, 22). Based on these findings, mutations within MATR3 RRMs are associated with severe disease onset in childhood while mutations within MATR3 IDRs are associated with adult-onset symptoms. MATR3 mutations are also associated with multisystem proteinopathy which impacts the central nervous system, muscles, and bones (23).

After identification of genetic links between MATR3, myopathy, and ALS/FTD, several studies reported on the prevalence of MATR3 mutations and pathology in disease. MATR3 pathology and clinical presentation in distal myopathy and ALS/FTD are reviewed elsewhere (23). Briefly, MATR3 displays cytoplasmic inclusions and decreased solubility, despite its expression levels being unaltered in distal myopathy (13, 95). Further, rather than the typical nuclear granular staining pattern, MATR3 wild-type and mutants display intense nuclear accumulation, diffuse cytoplasmic staining, and cytoplasmic inclusions in ALS neurons (14, 62, 96). Cytoplasmic redistribution and inclusion formation of TDP-43 and FUS is also common in ALS pathology (15, 16). Interestingly, MATR3 cytoplasmic inclusions are also positive for TDP-43, and the two proteins are known to interact in an RNA-dependent fashion (14, 96). TDP-43 inclusions are observed in 97% of ALS cases but only a subset of these are positive for MATR3 (96). A G_4C_2 hexanucleotide repeat expansion within the first intron of *C9ORF72* is the most common cause of familial ALS/FTD (97, 98). MATR3 cytoplasmic inclusions as well as colocalization with G_4C_2-RNA foci has been observed in C9-ALS/FTD, where MATR3 may genetically modulate C9orf72-mediated pathogenesis (99). Studies conflict on whether MATR3 expression levels are dysregulated in the spinal cord (96, 100). Adult muscle and central nervous systems have the lowest MATR3 expression levels and are seemingly most sensitive to MATR3 perturbation, whether that be due to mutation, mislocalization, or expression level dysregulation (12). As such, MATR3 is occasionally found in cytoplasmic inclusions in pathology, although this mislocalization is less common for MATR3 than it is for TDP-43 or FUS. It remains unclear why neurons and myocytes are the most sensitive to MATR3 mutations, or why some clinical presentations coincide with aging.

Cellular and Animal Models of MATR3 Dysfunction

Several model systems have been developed to investigate the underlying biology linking MATR3 dysfunction to ALS/FTD. Most studies have investigated the impact of the disease-associated mutations S85C and F115C, although recently the link between F115C and ALS/FTD was brought into question (94). Overexpression of MATR3 in yeast, fruit flies, or primary neurons is toxic, and knockdown of MATR3 in primary neurons is detrimental to cell survival, indicating that neurons are sensitive to any changes in MATR3 expression level (33). However, introduction of disease-associated mutations does not substantially modulate MATR3 toxicity (18, 33, 89, 101). Overexpression of MATR3 and F115C in mouse muscle elicited MATR3 pathology in both strains, and muscle atrophy and motor phenotypes were observed in the F115C strain (37). Overexpression of MATR3 and S85C in mouse muscle by AAV intramuscular injections induced similar myogenic changes, as did near basal expression of S85C under the CMV promoter (38). Additionally, MATR3 expression was dysregulated in a mutant SOD1 mouse model of ALS (102). In contrast, knock-in of F115C and P154S at the endogenous MATR3 loci did not result in motor

phenotypes or neuropathic changes in homozygous or heterozygous mutant mouse models (103, 104). Yet, homozygous knock-in of S85C at the endogenous MATR3 locus resulted in behavioral and neuropathic changes resembling early ALS while heterozygous knock-in did not lead to an altered phenotype (88). To further understand the sequence-based drivers of toxicity, using a series of deletion constructs it has been demonstrated that the MATR3 ZFs drive toxicity in primary neurons, while the MATR3 RRMs drive toxicity in yeast and *Drosophila* models. In sum, this evidence indicates that disease models are very sensitive to MATR3 expression levels, the MATR3:S85C mutation is most closely related to disease, and heterozygous MATR3 mutations alone may not drive pathogenesis.

Introducing disease-associated mutations does not largely alter the nucleocytoplasmic localization of MATR3 in yeast, CHO cells, or primary neurons (18, 33, 55). Studies in mammalian cells, *Drosophila*, and primary neurons have indicated the presence of higher levels of insoluble S85C compared to MATR3 (13, 14, 33, 89, 101). Additionally, S85C was found to have a longer half-life than MATR3 and is unable to be cleaved by neuronal protease calpain 1 in primary neurons (89, 105). S85C binds TDP-43 with higher affinity than MATR3 in HEK293T cells and colocalized aggregates of S85C with TDP-43 were observed in patient samples (14). In conditions where the interaction of MATR3 and RNA is altered, S85C disrupts condensate dynamics and morphology (18, 33, 44, 63). Though studies have conflicted on whether or not MATR3 localizes to stress granules (35, 55, 64), patient fibroblasts harboring the S85C mutation displayed disrupted stress granule formation and dynamics without MATR3 colocalization (95). Of the studied MATR3 disease-associated mutations, S85C has been the most well-characterized and shown to most substantially alter the solubility and phase properties of MATR3.

MATR3 is Implicated in a range of other disorders

While MATR3 missense mutations have only been associated with neuromuscular disorders, various other diseases have been linked to dysregulated MATR3 expression levels and aberrant interaction of MATR3 with nucleic acids. Altered MATR3 expression levels and cytoplasmic pathology has been noted in Alzheimer's disease patient samples and a mouse model of Alzheimer's disease (106, 107). MATR3 expression was also found to be downregulated in the fetal Down's syndrome brain (108). Differential MATR3 expression is also associated with depression, where MATR3 has been proposed as a potential biomarker (109). In heart disorders, as described above, increased MATR3 expression due to chromosomal translocation is associated with a congenital heart defect (87), and MATR3 regulates cardiomyocyte morphogenesis (81, 110). Further, increased MATR3 mRNA levels were observed in vascular tissue of patients with coronary artery disease as compared to healthy controls (111). All of this evidence indicates that central nervous system, heart, and muscle cells are particularly sensitive to perturbations in MATR3.

Dysregulation of MATR3 has also been associated with cancer. MATR3 levels were found to be decreased in clear cell renal carcinoma and non-small cell lung cancer, where it may have potential as a biomarker (112, 113). MATR3 levels were also decreased in breast cancer tumors where it may act as a tumor suppressor (113, 114). Phosphorylation of MATR3 by Src kinase, a strong tumor promoter, resulted in upregulated MATR3 expression

(115). Several other studies have also implicated MATR3 in cancer cell proliferation. In prostate cancer and neuroglioblastoma, MATR3 interacts with lncRNA *SNHG1* to regulate proliferation (116, 117). Reduced MATR3 expression resulted in decreased cancer cell proliferation due to decreased splicing of critical mitotic spindle factor CDC14B by MATR3 (43). MATR3 knockdown inhibited malignant melanoma proliferation (118) as well as induced apoptosis and altered colony formation in oral squamous cell carcinoma (119). Furthermore, MATR3 has been implicated in viral biology, where decreasing MATR3 levels in infected cells resulted in lower viral loads (120). Upon infection of human cells with HIV, MATR3 interacts with viral RNA to promote its nuclear export and has a role in controlling viral latency (121–124). The diverse disorders in which MATR3 dysfunction is implicated underscores the importance of MATR3 across biology and the need for further studies of MATR3 function and dysfunction.

Open Questions about MATR3

Studies of MATR3 have revealed its key roles in nucleic acid metabolism, as well as the consequences of its dysregulation, perhaps most notably its association with ALS/FTD pathology. However, we still generally lack a molecular understanding of MATR3 properties and functions. For instance, the critical binding residues of the MATR3 RRMs and the RNA sequence determinants for binding MATR3 have not been elucidated. Although over half of MATR3 is comprised of disordered regions, we do not understand how this disorder effects MATR3 properties and function. Phase separation is frequently driven by disordered protein regions, however, most evidence suggests that MATR3 phase separation is inhibited by physiological RNA binding. While MATR3 has been implicated in various nucleic acid metabolism and cell differentiation roles, it is unclear whether MATR3 directly interacts with these components or if these functions are dependent on MATR3 phase separation. Recent visualization of a nuclear network of MATR3 and RNA provides compelling evidence that may explain how MATR3 scaffolds chromatin organization and functions in cell differentiation (44, 76, 84). However, it remains unclear how the disordered nature of MATR3 contributes to the network architecture, whether this network is a rigid or dynamic structure, and what nucleic acid metabolic functions of MATR3 are dependent on network localization. Further investigation of the intrinsic material and nucleic acid binding properties of MATR3 would provide important foundational knowledge for understanding the function and dysregulation of MATR3.

Furthering our understanding of MATR3 features, phase properties, and functions will help us unravel the roles of MATR3 in disease. Muscle and neurons appear to be the cells most sensitive to MATR3 perturbations via mutation or dysregulated expression of MATR3. Despite efforts to understand how MATR3 is implicated in disease, it is unclear which properties, interactions, or functions of MATR3 are the key vulnerabilities that trigger disease pathogenesis. Some evidence suggests that MATR3 mutations dysregulate its phase properties, but the mechanism by which this might occur is unknown. It is also possible that the critical factors leading to disease pathogenesis are downstream of MATR3 dysregulation, such as disruption of transcripts regulated by MATR3 or aberrant recruitment of MATR3 into biomolecular condensates. Indeed, MATR3 has been shown to interact with TDP-43 and to modulate *C9orf72* hexanucleotide repeat expansion mediated neurodegeneration, both of

which are prominent drivers of ALS pathology. Characterizing the dysregulation of MATR3 properties and interactions in disease models of ALS/FTD may be crucial to unraveling the puzzle of ALS/FTD pathogenesis. Further, MATR3 may serve as a potential target that can be modulated with therapeutic RNA molecules to correct dysregulated condensate properties.

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Perspectives

- Matrin-3 is an intrinsically disordered RNA-binding protein that plays a number of key roles in nucleic acid metabolism, and its dysfunction is implicated in ALS/FTD, myopathy, and a number of other disorders.
- Currently it is thought that Matrin-3 functions similarly to other RNA-binding proteins implicated in ALS/FTD, including TDP-43 and FUS. It is thought that Matrin-3 localizes to biomolecular condensates under physiological conditions, however Matrin-3 also has distinct features such as its lack of a prion-like domain, and so its condensate properties remain unclear.
- In future studies, it will be important to better understand the molecular basis for RNA binding by Matrin-3, which may inform the development of new therapeutics. It will also be important to better understand how the highly disordered nature of Matrin-3 effects its function and dysfunction.

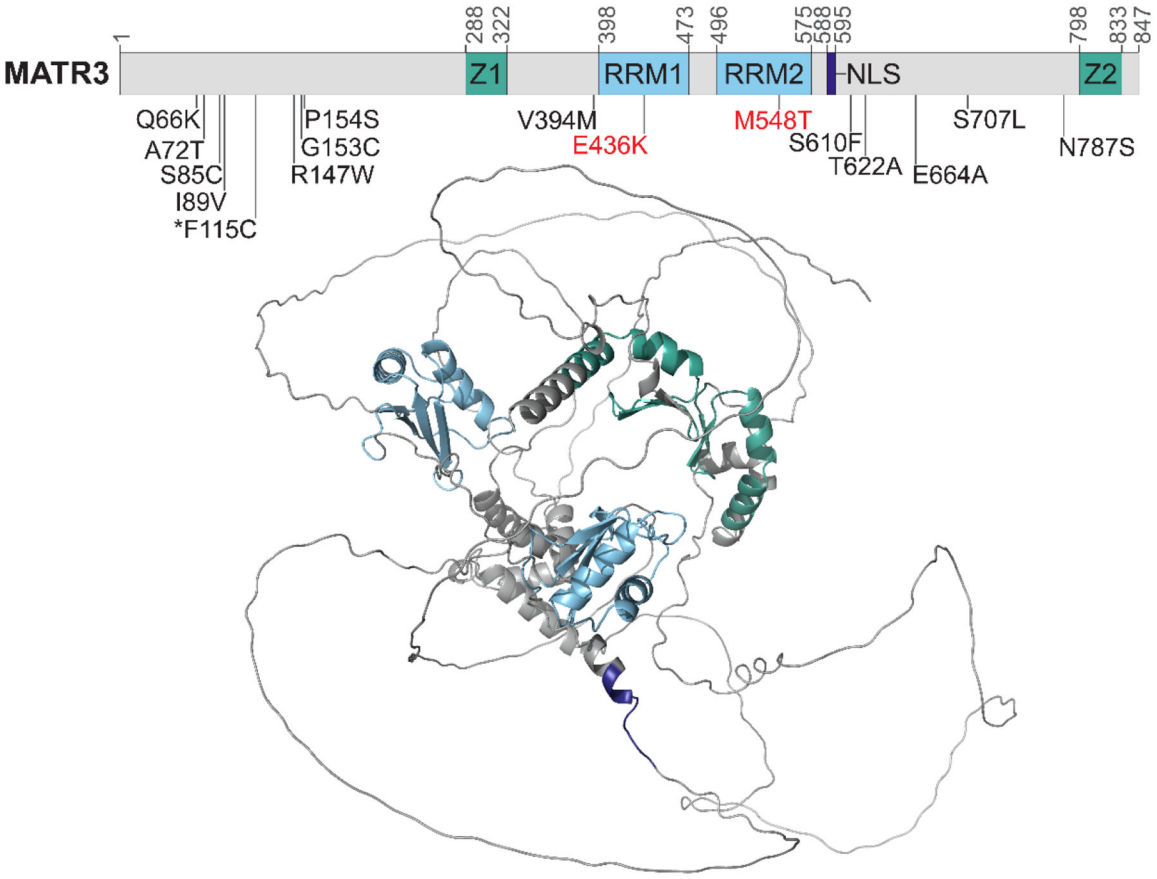

Figure 1:

MATR3 is a disordered DNA- and RNA-binding protein. (Top) Domain map of MATR3. The zinc finger motifs (Z1–2), RNA recognition motifs (RRM1–2), and nuclear localization sequence (NLS) are highlighted. Adult-onset neurological disorder associated mutations are shown in black, childhood-onset neurological disorder associated mutations are shown in red, and * indicates a patient-associated mutation which may not be causative of disease. (Bottom) Cartoon structure of human MATR3 predicted by Alpha Fold with RRMs shown in blue, zinc fingers shown in teal, and NLS shown in navy.

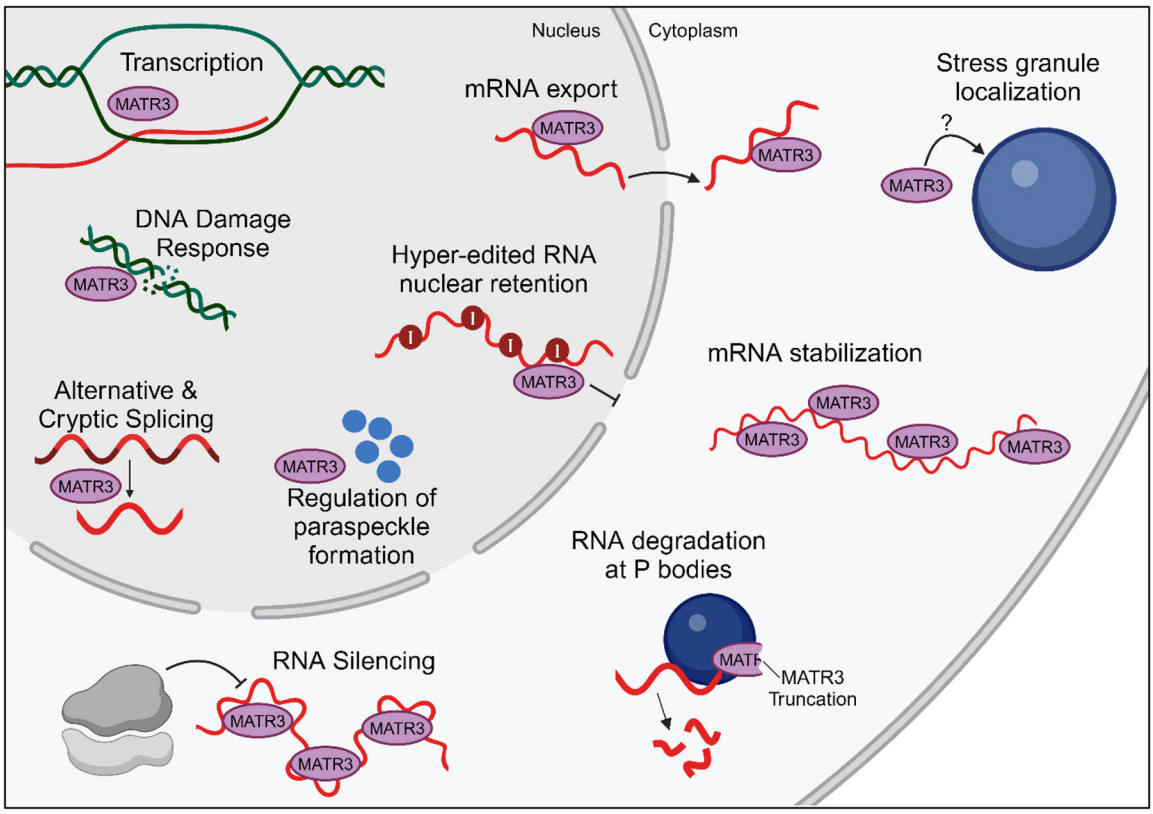

Figure 2:

Involvement of MATR3 in physiological processes. Cellular view of MATR3-linked processes. In the nucleus, MATR3 is implicated in transcription, DNA damage response, splicing, mRNA export, nuclear retention of hyper-edited RNA, and regulation of paraspeckle formation. In the cytoplasm, MATR3 is implicated in RNA silencing, RNA degradation at P bodies, mRNA stabilization, and may localize to stress granules.

Table 1:

Documented MATR3 variants associated with disease. Indicated variants include point mutations, splicing variants, and a chromosomal translocation. The region of MATR3 which is affected and the associated diseases are indicated.

Variant	Region Affected	Disease	References
p.Q66K	IDR	ALS	(27)
p.A72T	IDR	ALS	(26)
p.S85C	IDR	ALS/myopathy	(13, 14)
p.I89V	IDR	ALS	(26)
p.F115C	IDR	*ALS/dementia	(14, 94)
p.R147W	IDR	ALS	(28)
p.G153C	IDR	ALS	(27)
p.P154S	IDR	ALS	(14)
p.V394M	IDR	ALS	(25)
p.E436K	RRM	Early-onset neurodegeneration	(21)
p.M548T	RRM	Neurodevelopmental defects	(22)
p.S610F	IDR	ALS	(30)
p.T622A	IDR	ALS	(14)
p.E664A	IDR	ALS	(26, 27)
p.S707L	IDR	ALS/FTD	(27)
p.N787S	IDR	ALS	(26, 27)
c.48+1G>T	Alternative start coding exon	ALS	(25)
c.−339+2T>A	Noncoding exon 2	ALS	(25)
46,XY,t(1;5)(p36.11;q31.2)dn	3’ untranslated region	Congenital heart defects	(87)

*An additional mutation identified in a different protein in the same kindred, pathogenicity of MATR3 mutation is in question.