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The Relationship of Prions and Translation

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Summary

Prions are infectious proteins, without the need for an accompanying nucleic acid. Nonetheless, there are connections of prions with translation and RNA, which we explore here. Most prions are based on self-propagating amyloids. The yeast [PSI⁺] prion is an amyloid of Sup35p, a subunit of the translation termination factor. The normal function of the Sup35p prion domain is in shortening the 3' polyA of mRNAs and thus in mRNA turnover. The [ISP⁺] prion is so named because it produces anti-suppression, the opposite of the effect of [PSI⁺]. Another connection of prions with translation is the influence on prion propagation and generation of ribosome-associated chaperones, the Ssb's, and a chaperone activity intrinsic to the 60S ribosomal subunits.

Keywords

prion; amyloid; parallel in-register; chaperones; Sup35; mRNA turnover; translation termination

Prions are infectious proteins that do not require an accompanying nucleic acid to transmit a disease or a trait. Prions of mammals include the uniformly fatal transmissible spongiform encephalopathies, such as scrapie of sheep, Creutzfeldt-Jakob disease of humans, bovine spongiform encephalopathy and chronic wasting disease of elk and deer. These diseases are amyloidoses of PrP, a cell surface protein of uncertain function (reviewed in (1,2)). The recognition that [URE3] and [PSI⁺], two long-known cytoplasmic genetic elements of *S. cerevisiae* (3,4), are prions of Ure2p and Sup35p, respectively (5), accelerated progress in the prion field. Yeast and filamentous fungi are now known to have a number of amyloid-based prions and two prions based on enzymatic processes (Table I).

Yeast prions can determine phenotypic traits which, in many cases, were the basis of their discovery. Amyloid formation by the Ure2 protein makes it inefficient at repressing the genes encoding enzymes and transporters needed for using poor nitrogen sources when a good nitrogen source is available. Derepression of *DAL5*, encoding the allantoin transporter, is used to detect the [URE3] prion. Sup35p is a subunit of the translation termination factor, and its amyloid formation in [PSI⁺] cells makes it inefficient resulting in increased readthrough of termination codons.

Not all prions involve amyloid. The [β] prion of *S. cerevisiae* is simply the active form of the vacuolar protease B, which, in the absence of protease A, can activate (and is needed to activate) its own precursor (6,7). Cells without the active protease B remain so, and those with it propagate this activity by converting the inactive precursor to active form. The active form is infectious, and this system has all the genetic properties expected for a prion. The [C] trait of *Podospora* appears to be similar, possibly involving self-phosphorylating MAP kinases as the basis of the trait (8).

In this review, we briefly survey the growing menagerie of prions, and explore the connections of prions with translation and RNA. Although the fundamental prion

phenomenon is one of protein-protein interaction, there are several interesting interactions of the translation process and prions.

Structural basis of yeast prions

Each prion protein has a prion domain, a limited part of the protein which is sufficient to transmit the prion *in vivo*, and whose amyloid form made from recombinant protein can infect yeast cells with the prion (9–14). In amyloid formed by the full length Ure2p, for example, the prion domain has changed from being unstructured to the highly structured amyloid form, while the rest of the molecule is essentially unchanged (15–18). Amyloid formed by the prion domains of Ure2p, Sup35p and Rnq1p each have an in-register parallel beta sheet architecture with folds of the sheet along the filament axis (Fig. 1)(19–21). Thus, the surface of the prion filaments have strips of aligned amino acid residues: a line of glutamines or asparagines can form the "polar zipper" - a line of hydrogen bonds between the amide side chains that stabilize the structure (22–24), a line of serine or threonine residues can form pairwise hydrogen bonds, a line of a hydrophobic residue will likewise have positive interactions. It is suggested that variation in the location of the folds and the extent of the beta sheet may be the points of difference among prion variants.

This structure suggests a mechanism by which information is inherited by a protein – how a protein can act as a gene (25). The prion domains are unstructured, and acquire the structure of the molecules in the amyloid filament as they add on to the end. The favorable interactions between adjacent identical residues on the last molecule that is part of the filament and the newly joining molecule - the polar zippers, other hydrogen bonds along the filament, and hydrophobic interactions – direct the new molecule to change from being unstructured to having the structure of the molecules in the filament. Segments forming beta strands in the filament molecules will be beta strands in the new molecule; turns in the filament will be turns in the new molecule (Fig. 1)(25). Thus the prion form templates the conformation of new prion protein monomers joining the filament, just as parental DNA strands template the sequence of new DNA strands.

Biological roles of yeast and fungal prions

While mammalian prions are uniformly fatal, yeast and fungal prions are compatible with continued growth, and it has been suggested that some may be advantageous to their hosts (26–28). Plate tests of growth under various conditions cannot tell whether prions are beneficial or detrimental without knowledge of the distribution of the conditions tested in the ecological niche of yeast (29). It was suggested that [PSI+] was a general advantage under stress conditions, or at least at high temperature or high ethanol conditions (27). In another report, the effect of [PSI+] on tolerance to ethanol, heat or other stresses varied with yeast strains (28). A third group, using the same strains as the second group, found mostly different results (30).

How then can one determine if a prion is beneficial or detrimental? Deleterious viruses, plasmids, bacteria and prions (e.g. scrapie and chronic wasting disease) are easily found in the wild. Their infectivity allows them to spread faster than the damage they cause to their hosts selects against their abundance. Certainly an infectious element that is advantageous would be everywhere. In fact, the [URE3] and [PSI+] prions are not found in any of the wild strains surveyed (31), indicating that these prions are diseases of yeast. Whether transient variants of yeast prions could have beneficial phenotypes has not been reported. In contrast, 80% of wild strains carry the [Het-s] prion, suggesting that it is a benefit to its host (32). Indeed, the heterokaryon incompatibility function provided by the [Het-s] prion is known to be advantageous to the host. However, [Het-s] is the basis for a meiotic drive phenomenon

(where a gene promotes its own inheritance by disabling gametes with other alleles, rather than benefiting its host), so that even in this case, the prion may be a disadvantage (32).

While rather few species have been examined, the ability of the N-terminal domains of Ure2p from other species to support prion formation seems to be sporadic (33,34)[H.E. Edskes, A. Engel & R. Wickner, in preparation], suggesting that prion formation is not preserved in evolution, but is rather the price yeast pays for another function. In fact, the prion domain prevents the rapid turnover of the Ure2 protein and so is necessary for efficient nitrogen catabolite repression (35). Similarly 25% of wild strains of *S. cerevisiae* examined had a large deletion in their Sup35 prion domains preventing them from becoming [PSI+], indicating that prion formation in this case as well is not conserved even within *cerevisiae* (36). The Sup35p prion domain also has a function that is unrelated to prion formation, being necessary for the normal process of mRNA turnover through a role in shortening of the mRNA's 3' polyA (37) (see next section).

Sup35p roles in translation termination, mRNA turnover and prion formation

Sup35p/eRF3 is, with Sup45p/eRF1, a subunit of the translation termination factor. Sup45p recognizes stop codons and activates the ribosome's cleavage of the peptide-tRNA bond. Sup35p, through its GTPase activity, stimulates Sup45p (38–40). Prion formation by Sup35p (the [PSI+] prion) is detected by increased readthrough of premature termination codons (3). One example of this pathology is elevated readthrough of the "shifty stop" codon controlling antizyme, a protein that targets ornithine decarboxylase for degradation and thereby controls polyamine biosynthesis (30). While deletion of the Sup35p N-terminal prion domain does not affect the efficiency of translation termination (as judged by readthrough of premature termination codons) (41), the presence of the prion domain does enhance readthrough in the context of a number of mutations in the C-terminal domain (42).

The Sup35p N-terminal prion domain also interacts specifically with Pab1p, the polyA binding protein (43,44). Deletion of the Sup35 prion domain lengthens the half-life of the various mRNAs tested, both native yeast messages and foreign mRNAs (37). This mRNA lifetime expansion is accompanied by an increase in the mean mRNA polyA length, indicating that the Sup35p prion domain has a role in the polyA shortening process that precedes, and is a signal for mRNA decay. This interaction is not specific to the *S. cerevisiae* Sup35p N-terminal domain, and was actually first documented for the human Gsp/Sup35 N-terminal domain (43). These results indicate that the Sup35 prion domain is not simply there to enable the cell to form prions. Rather, the Sup35p prion domain has a normal function in mRNA turnover through its role in 3' polyA shortening.

[ISP+] may be a prion of Sfp1p, a regulator of ribosome biogenesis

[ISP+] is a non-chromosomal genetic element that gets its name from having the opposite effect to that of [PSI+], namely it confers antisuppression (45). As discussed above, Sup35p is a subunit of the translation termination factor, and thus mutations of *SUP35* have a suppressor effect, that is, a termination codon is not promptly recognized as such because of a deficiency of normal termination factor, and there is more time for a mistranslation event to occur, such as the pairing of a suppressor tRNA to the stop codon. The *sup35-10* and *sup35-25* missense mutants have such a suppressor effect with the nonsense mutants, *his7-1* and *lys2-87*. Volkov et al. noted that after culturing strains containing these suppressible mutations and *sup35-10* or *sup35-25*, they often found that the strains had lost the suppressor effect of the *sup35* mutation. This antisuppressor effect was frequently eliminated by growth in the presence of guanidine HCl, but unlike curing of [PSI+] or

[URE3], concentrations of > 5 mM were needed to observe curing, and the efficiency of curing was rather low (45). From a cured strain ([isp⁻]), it was possible to again isolate [ISP⁺] derivatives. Such “reversible curing” is one of the classical genetic criteria for identifying a prion (5).

On crossing an [ISP⁺] antisuppressor – carrying strain with an [isp⁻] (guanidine-cured) strain (both carrying the *sup35-10* or *sup35-25* mutation and the suppressible *his7-1* and *lys2-87* alleles), the meiotic spore clones showed 4antisuppressed : 0 segregation, and each of these antisuppressed spore clones could be cured of the antisuppression by growth in guanidine (45). [ISP⁺] could also be transferred to an [isp⁻] strain by cytoduction (mating followed by cytoplasmic mixing but without nuclear fusion), but only 16% of cytoductants received the [ISP⁺] element (45). Guanidine curing of [PSI⁺] has been shown to be due to the inhibition of Hsp104 (46), but [ISP⁺] was not cured by either deletion of *HSP104* or by its overexpression (45). Although the [ISP⁺] genetic element is manifested through its effects on *sup35* mutants, propagation of [ISP⁺] does not depend on the Sup35p prion domain, nor does overexpression of Sup35p increase the frequency of [ISP⁺] appearance in an initially [isp⁻] strain (45).

Recently, it has been shown that propagation of [ISP⁺] depends on the Sfp1 protein (47), a transcription factor controlling ribosome biogenesis (48). "Thus [ISP⁺] is apparently a prion of Sfp1p, and the involvement of Sfp1p in controlling ribosome biogenesis implies that it could affect suppression efficiency."

Mammalian prions, translation and RNA

Propagation of the PrP-based transmissible spongiform encephalopathies involves conversion of PrP^C, a cell - surface, glycoposphatidylinositol-anchored protein, to PrP^{Sc}, an amyloid form of the protein. This conversion process occurs on the cell surface, or in endosomes, long after the translation process (49). An *in vitro* prion propagation system has been developed, reminiscent of the polymerase chain reaction, in which PrP^{Sc} serves as template for polymerization of amyloid starting with brain extracts containing PrP^C. In this system, RNA stimulates the reaction, but this effect is not sequence specific, and even polyA can serve this purpose (50).

An internal ribosome initiation site in *URE2* can affect [URE3]

The prion domain of Ure2p extends from about residues 1 to 65 or 70 as judged by the part that is sufficient for prion induction (10) or the portion that becomes protease - resistant in amyloid of Ure2p (16). However, the Q/N rich property extends to about residue 89 and the structured C-terminal domain begins at about residue 97 (51)(52). Ure2p begins with a pair of methionine residues, and the third methionine occurs at residue 94.

Komar et al. have shown that initiation occurs at the residue 94 with a significant frequency (53). The Ure2p^{94–354} fragment represented about 20% of Ure2 protein in extracts of wild-type strains, but changing of codon 94 from AUG to CTT eliminated this fragment, indicating that it was not due to translation of a minor transcript or to degradation of the unstructured prion domain (53). Inserting *URE2* ORF nt 203–368 (encoding amino acids 68–122) into a bicistronic vector confirmed that *URE2* contains an internal ribosome entry site (IRES) promoting cap-independent translation. Because Ure2p lacking the prion domain is more rapidly degraded (35), the real frequency of initiation at Met94 may be higher than it appears.

Overproduction of the C-terminal domain cures [URE3] (54). Replacing the normal cap-binding protein, eIF4E, with a temperature sensitive version, increased the fraction of Ure2p

starting at Met94 to near 50% and destabilized the [URE3] prion. In addition, the 94AUG to CTT mutation results in the high frequency spontaneous development of the [URE3] prion (53). These results suggest that the presence of the *URE2* IRES keeps down the frequency of [URE3] generation.

While the data in Komar et al. seems clear, it should be mentioned that Shewmaker et al. did not detect the 30 kDa Ure2 species in normal cells using a genomic copy of Ure2p with a C-terminal HA epitope tag (35). Moreover, we do not observe high frequency [URE3] generation or the [URE3] prion phenotype in the *URE2* 94AUG->CTT mutant (unpublished results).

Ribosome-associated chaperones in prion generation and propagation

The Hsp70 superfamily of chaperones includes the Ssb group, in yeast comprising two nearly identical proteins largely associated with ribosomes in polysomes, and believed to facilitate folding of nascent polypeptides (55). Chernoff et al. have shown that Ssb1p and Ssb2p have antagonistic activities toward propagation and generation of [PSI⁺](56). Overproduction of the disaggregase Hsp104 cures [PSI⁺] and concomitant overproduction of Ssb1p increases the curing efficiency. In fact, overproduction of Ssb1 alone can cure [PSI⁺] (57). The *ssb1Δ ssb2Δ* double mutant also shows a considerably increased frequency with which [PSI⁺] arises *de novo*. (56). These results suggest the possibility that nascent (ribosome-associated) Sup35p may be able to associate with the growing amyloid filaments, but there is no direct evidence for this. Note that although the Ssb proteins are ribosome-associated, conversion of Sup35p to the prion form need not occur co-translationally (58).

Another ribosome-associated chaperone activity is an activity of the large subunit rRNA itself (59). For example, the *E. coli* 23S rRNA can renature lactate dehydrogenase in a reaction inhibited by the ribosome-active antibiotics chloramphenicol and erythromycin.

Blondel embarked on a search for treatments for mammalian prions by screening compounds for curing of the yeast prions [PSI⁺] and [URE3], and then testing promising candidates in scrapie-infected tissue culture cells and mice (60). Remarkably, he found that several compounds active against yeast also cleared tissue culture cells of scrapie infection and prolonged survival of scrapie-infected mice (61). Affinity columns made with two drugs identified in this screen, 6-aminophenanthridine (6-AP) and guanabenz (GA), each bound ribosomes, while similar drugs inactive against prions did not. While neither drug affected translation *in vivo*, both inhibited the ribosome - associated chaperone activity of *S. cerevisiae* ribosomes, measured by its ability to renature carbonic anhydrase (62). This work is important both in providing a potential avenue toward treatment of the thus far intractable prion diseases, and a new approach to the incompletely characterized ribosomal chaperone activity.

While the intricate interactions of many chaperones of various classes with prions (reviewed in (63)) make it perhaps no surprise that a ribosomal chaperone activity should affect prion propagation, it is not yet clear whether this activity is important during the synthesis of the prion proteins, or is acting independent of translation. Moreover, the current evidence does not unequivocally rule out the possibility that the prion - blocking and rRNA chaperone inhibition activities of these drugs are separate actions of a single compound.

Cytoplasmic polyadenylation factor is speculated to be a prion in yeast

The marine snail *Aplysia* is used in studies of learning because of its large neurons and relatively simple nervous system (64). Translation is believed to play a role in synaptic plasticity, the changes in synapses consequent to their repeated stimulation that are believed

to have a role in memory. The cytoplasmic polyadenylation element binding factor (CPEB) regulates mRNA polyadenylation, and thus translation, in many vertebrates and invertebrates by binding to a 3' UTR site called CPE along with Maskin, Symplekin, CPSF and other factors required for the regulation (65). When CPEB is activated by specific kinases, it induces polyadenylation of the mRNA to which it is bound by a cytoplasmic polyA polymerase. CPEB appears to be involved in mediating synaptic plasticity (65). The presence of a Gln/Asn-rich sequence in the N-terminal part of *Aplysia* CPEB, resembling yeast prion domains, led to speculation that prion formation by CPEB might have a role in memory.

To test this speculation, the ability of CPEB to act as a prion in *S. cerevisiae* was examined (66). The CPE site was placed in the 3' UTR of *lacZ* in yeast, and it was reported that this construct was only expressed when CPEB was also expressed and was in an aggregated form, and that mRNA levels were independent of CPEB expression or aggregation in this yeast system (66). However, there are no yeast homologs of Maskin or Symplekin, nor does yeast have a cytoplasmic polyA polymerase, so it is unlikely that CPEB could have its normal function in yeast. While non-polyA mRNAs are stable in *Xenopus* oocytes in which many of the original CPEB mechanism studies were done, yeast mRNAs lacking polyA are rapidly degraded (e.g., (67)). While aggregation of CPEB was observed in some cells and not in others, the evidence that this was a prion phenomenon was incomplete. For example, does overproduction of CPEB increase the frequency with which the putative prion arises? Moreover, deletion of the Q/N-rich putative prion domain did not affect the activation of CPEB. It is also paradoxical that aggregation was necessary for CPEB action. One would expect that, as in the case of Sup35p, aggregation would impair ability to reach the mRNAs where the action must occur. Clearly, further work will be necessary to establish whether CPEB can act as a prion in yeast.

Conclusions

While the prion phenomenon is primarily one of protein misfolding, it is clear that there are several connections with RNA and translation. Two prions primarily affect translation, and several have effects on transcription, but of course a prion could, in principle, affect any process a protein can affect. The translation – associated chaperones, both the intrinsic ribosomal chaperone activity and the ribosome-associated Ssb Hsp70s, have important effects on prion generation and propagation. The detailed mechanisms of each will doubtless be of increasing interest and there is a prospect of prion therapies based on drugs affecting ribosomal chaperones. Since the folding of proteins during and immediately after synthesis is a dicey process, it seems inevitable that more connections will be found between this process and the misfolding of prion proteins.

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Fig. 1. In-register parallel β -sheet structure explains how prions transmit their conformation to the normal form of the protein

The unstructured prion domain of monomers are forced to assume the conformation of the protein in the amyloid filaments by interactions with the main chain and side chain parts of the identical residues of the protein.

Fig. 2. Prions and translation

The Sup35 prion protein is a component of the translation termination factor, and is necessary for the shortening of the 3' polyA of mRNAs that is a stage in mRNA degradation. The ribosome-associated Ssb1 chaperone protein and the chaperone activity of the 60S ribosome subunits also affect prion generation and propagation. The [ISP+] prion also affects translation by an as yet unknown mechanism.

Table 1

Prions

Prion	Organism	Protein	Protein function or phenotype	Ref.
<i>Amyloid-based prions</i>				
TSEs	mammals	PrP	non-essential, function unclear	(1,2)
[URE3]	<i>S. cerevisiae</i>	Ure2p	nitrogen catabolism regulator	(5)
[PSI+]	<i>S. cerevisiae</i>	Sup35p	translation termination factor	(5)
[PIN+]	<i>S. cerevisiae</i>	Rnq1	rare priming of other prions	(68)
[SWI+]	<i>S. cerevisiae</i>	Swi1p	transcription factor	(69)
[MCA]	<i>S. cerevisiae</i>	Mca1	metacaspase homolog	(70)
[OCT]	<i>S. cerevisiae</i>	Cyc8p	transcriptional co-repressor	(71)
[Het-s]	<i>P. anserina</i>	HET-s	heterokaryon incompatibility	(72)
[ISP+]	<i>S. cerevisiae</i>	?Sfp1	antisuppression	(47)
[MOT]	<i>S. cerevisiae</i>	Mot3p	transcription factor	(73)
<i>Enzyme activity-based prions</i>				
[BETA]	<i>S. cerevisiae</i>	Prb1	active vacuolar protease B	(7)
[C]	<i>P. anserina</i>	MAP kinases	'crippled growth'	(8)