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Prions of Fungi: Inherited Structures and Biological Roles

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Abstract

PREFACE—The term 'prion' means an infectious protein that does not need an accompanying nucleic acid. There are six fungal prions, including four self-propagating amyloids and two enzymes that are necessary to activate their inactive precursors. Here we explore the scope of the prion phenomenon, the biological and evolutionary roles of prions, the structural basis of the amyloid prions, and the prominent role of chaperones (proteins that affect the folding of other proteins) and other cellular components in prion generation and propagation.

INTRODUCTION

The uniformly fatal mammalian transmissible spongiform encephalopathies (TSEs) were first widely recognized as scrapie of sheep in western Europe in the 1700s[1], but may have existed much earlier[2]. The colourful history of the TSEs (Box 1) led to the widely[3], but not universally[4], accepted notion that these diseases are transmitted by a protein, without the need for an accompanying nucleic acid. Such an agent is called a prion, and the TSEs are believed to be caused by an amyloid (Glossary) form of the PrP protein. The known prions are altered forms of cellular proteins that are able to convert the unaltered form into the altered form. This positive-feedback feature is the basis for the self-propagation and infectivity of prions.

BOX 1: Early history of prions

~1000 B.C. Chinese character might suggest scrapie?

~1730 Earliest records of scrapie (die Reiberkrankheit, Ger.; la prurigo lombaire, Fr.; surlokor, Hung.) in Europe.

1920's Creutzfeldt, Jakob, … describe human spongiform encephalopathies

1936 Cuille and Chelle transmit scrapie from sheep to sheep by innoculation

1939 Propagation to goats: first trans-species transmission

1952 [Het-s] non-Mendelian gene of *Podospora* (Rizet)

1957 Zigas & Gajdusek describe Kuru among the cannibal Fore tribe of New Guinea

1959 Wm. Hadlow suggests Kuru similar to scrapie based on pathology

1960 Scrapie transmitted to mice (Chandler)

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1965 [*PSI*+] non-Mendelian gene of yeast (Cox)

1966 Gibbs & Gajdusek show Kuru & CJD is infectious to monkeys: 'slow virus'

1966 Alper shows scrapie agent very UV - resistant. "Does the agent of scrapie replicate without nucleic acid?"

1967 Griffith suggests the prion mechanism essentially in its modern form!

1968 Dickinson describes *Sinc* (for scrapie incubation period) gene of mice. Later shown to be the PrP gene.

1971 [URE3] non-Mendelian gene of yeast (Lacroute)

1982 Prusiner purifies scrapie agent; names main protein PrP; coins term 'prion'

1985 Weissmann and Chesebro clone PrP gene of hamster and mouse

1986 Carlson & Prusiner: *Sinc* = PrP gene

1986 First case of BSE described (Wilesmith)

1989 Owen, Hsiao, Collinge & Prusiner: inherited CJD associated with mutant PrP gene

1993 Weissmann makes PrP knockout: cannot propagate scrapie, mice normal

1994 Cytoplasmic genes of yeast [URE3] and [PSI+] are prions (Wickner)

1996 First cases of nvCJD described (Collinge)

The properties expected for fungal prions were deduced from the known nature of infection by fungal viruses and from the concept of an infectious protein[5]. Fungal viruses are non-chromosomal genes or genetic elements transmitted from cell to cell by cytoplasmic mixing due to cell fusion in the process of sexual mating or asexual fusion of cellular processes[6]. Fungal prions are also expected to be non-chromosomal (cytoplasmic) genetic elements[5]. It was reasoned that fungal prions must have three genetic traits that are not found (and are not expected to be found) for nucleic acid replicons[6]. First, if a prion can be cured (Glossary), it can nonetheless arise again *de novo* in the cured strain because the protein is still present in the cell and can again (although it happens rarely) undergo the prion change. Second, transient overproduction of the protein should increase the frequency with which it undergoes the change to the prion form, simply because there is more of it to change, and once the change has occurred it propagates to the other molecules of the same protein. Third, for prion that are inactive forms of a normally active protein, the phenotype of mutants in the gene encoding the protein (which is necessary for the propagation of the prion) should be similar to that of the presence of the prion form, as in each case the normal form is deficient[5]. Two non-chromosomal genetic elements of *Saccharomyces cerevisiae*, [URE3] and [*PSI*+], whose molecular basis had long been mysterious, both satisfied all three of these genetic criteria for prions[5], therefore initiating the fungal prion field. There are six known fungal prions, including four self-propagating amyloids and two enzymes; in this Review we will describe these prions, the identification of several with amyloids (therefore furthering their relationship to the mammalian prions), what is known about the amyloid structures, the roles of other cellular components and the biological roles of fungal prions.

SPECIFIC FUNGAL PRIONS

[URE3] and [*PSI*+], which are both non-chromosomal genes of *Saccharomyces cerevisiae*[7, 8], were shown to be prions of Ure2p and Sup35p (TABLE 1› FIG. 1), respectively, based on the three genetic criteria discussed above[5]. Ure2p is a regulator of nitrogen catabolism, repressing genes for the enzymes and transporters needed for using poor nitrogen sources,

when a good source is available[9]. The [URE3] prion, similar to a *ure2* mutation, results in inappropriate expression of (among many other genes) *DAL5*, which encodes the allantoate transporter, and this expression is usually used to indicate the presence of the [URE3] prion[8,10–12].

Sup35p is a translation-termination factor of *S. cerevisiae*, and, similar to *sup35* mutations, the [PSI+] prion results in increased read-through of termination codons[7]. The *ade2-1* premature termination mutation with the weak serine-inserting *SUQ5* suppressor tRNA or the *ade1-14* nonsense mutant are adenine auxotrophs, but also accumulate a red pigment due to oxidation of an accumulated precursor. This red color is useful in genetic tests for [PSI+][7] and has been adapted to the [URE3] system as well in the form of *DAL5-ADE2* fusion genes[11,12].

The [PIN+] non-chromosomal gene was identified by its requirement for induction of [PSI+] by overproducing Sup35p[13], and is a self-propagating amyloid of Rnq1p[14] (FIG. 1). Rnq1 means rich in N and Q residues, and this protein carries out a self-propagating aggregation *in vivo*, before its relationship to the [PIN+] gene was known[15]. Deletion of *RNQ1* does not produce any known phenotype[15].

[Het-s] was first described as a non-chromosomal gene necessary for the heterokaryon incompatibility in the filamentous fungus *Podospora anserina*[16]. In this process, two converging fungal colonies carry out trial fusion of cellular processes and test the identity of alleles at a dozen polymorphic loci (called *het* loci) to limit fusion to genetically identical individuals[17,18]. The *het-s* locus has alleles *s* and *S*, approximately equally represented in the population, and fusion of *het-s* and *het-S* hyphae leads to incompatibility, but only if the [Het-s] non-chromosomal gene is present. The [Het-s] non-chromosomal gene has the genetic properties expected of a prion of the HETs protein encoded by the *het-s* allele[19].

The prion concept is not limited to amyloids. An enzyme for which the active form is necessary for activation of its own inactive precursor can also be a prion[20]. The [β] prion in *S. cerevisiae* is the self-activating vacuolar protease B[20]. Protease B is made as an inactive precursor for which cleavage (by mature protease B) activates it[21,22]. The [β] prion is necessary for meiosis in yeast and for optimal survival in stationary phase[20]. In *P. anserina*, a non-chromosomal gene called [C], for 'crippled growth' is apparently based on a self-activating MAP kinase cascade[23].

THE AMYLOID OF PRION PROTEINS

Infection with amyloid of recombinant proteins

Amyloid is a filamentous and typically protease-resistant protein structure with a ‘cross-β-sheet’ architecture, meaning that the β-strands of the β-sheet run perpendicular to the long axis of the filaments (FIG. 2). A great deal of evidence indicated that [*PSI*+], [URE3], [Het-s] and [*PIN*+] are amyloid forms of Sup35p, Ure2p, HET-s and Rnq1p, respectively (reviewed in[24]). Each of these prions has now been shown to be transmissible to uninfected cells by the introduction of amyloid formed *in vitro* from the corresponding recombinant protein. For [Het-s], nearly 100% of colonies subjected to "gene gun" **[G]** introduction of amyloid HETs protein became infected, but only background rates are obtained with soluble protein or heat-denatured or acid-denatured aggregates[25]. Distinct prion variants of [PSI+] (see below) were faithfully transmitted by infection with amyloid formed from recombinant Sup35p primed with amyloid seeds from extracts of distinct strains[26]. Different *in vitro* conditions of amyloid formation can also lead to distinct amyloid variants, which are transmitted to cells by infection as prion variants[27]. [URE3] can likewise be transmitted to cells by infection with amyloid of Ure2p, but only rarely by soluble Ure2p[12]. Amyloid of recombinant Ure2p was nearly as infectious as extracts of [URE3] strains, and no infectivity was present in particles smaller than about 40-

mers[12]. Recently transmission of [PIN+] to yeast by amyloid of Rnq1p has similarly been documented[28].

Shuffled prion domains can still be prions

The prion domain of Ure2p is the Gln(Q)/Asn(N)-rich N-terminal 65 to 89 residues that is unstructured in its native (soluble) form [29,30]. Sup35p is comprised of a Q/N-rich N-terminal 123 residue prion domain (N), a 130 residue highly charged domain (M) and a C-terminal domain sufficient for translation termination (C)[31]. Point mutations in N[32,33], like single amino acid polymorphisms of PrP[34] can block the propagation of prions, even though both protein sequences can form prions themselves[35]. This sequence-specificity for prion transmission, long known in studies of the species barrier in mammals[36,37], suggests a relationship between apposed residues in the amyloid β-sheets that constitute the infectious material[38].

Surprisingly, random shuffling of the prion domains of Ure2p or Sup35p did not prevent the formation of prions by the shuffled proteins[39,40]. These results showed that for Ure2p and Sup35p it is the amino acid composition of the prion domain, not its sequence, that determines its ability to form a prion. Any complementarity or similarity between paired residues in an antiparallel β-sheet or a β-helix would certainly be destroyed by random shuffling. However, the pairing of identical residues in a parallel in-register β-sheet (see Glossary) would remain possible in the shuffled sequence[38,41]. Therefore, shuffleability of a prion domain suggests it has a parallel in-register β-sheet structure.

Parallel in-register β-sheet structure of Sup35NM

Solid-state nuclear magnetic resonance (NMR) has been crucial in elucidating the structure of amyloids[42]. Tyrosine residues are scattered throughout the prion domain (N) of Sup35p, and none are in the adjacent highly charged M domain. Using ^{13}C-1-tyrosine labeled amyloid of Sup35NM, solid-state NMR experiments showed that the distance from one labeled tyrosine to its next closest tyrosine neighbor was about 5 Å, approximately the 4.7 Å distance between β-strands[43]. This result strongly supports the parallel in-register β-sheet model for Sup35NM amyloid (Fig. 2). Although the N domain is sufficient to propagate [PSI+][31], labeling leucine residues, which are largely in the M domain, showed that they too were largely in parallel in-register β-sheet structure[43].

X-ray diffraction analysis of an amyloid - like structure formed by a seven-residue peptide from Sup35N, GNNQQNY, showed a parallel in-register β-sheet structure, the first atomic-level structure of an amyloid[44]. However, small fragments of other amyloids may have architectures different from the full peptide. Using pyrene maleimide modification, another study proposed a β-helix structure for Sup35NM[45], but the large probe size (~10 × 5 Å) may have affected the outcome. A β-helix involves β-bonds within each molecule, which is inconsistent with the solid-state NMR results[43] and with mass per length measurements[46].

The parallel in-register β-sheet structure implies that each residue of the prion domain is in intimate contact with the same residue of the adjacent molecules in the filament. This provides a simple templating mechanism for the transmission of prion variant information, which is presumed to be a difference in amyloid structure, during growth of the filament.

The prion domain of HETs is the C-terminal residues 218–289[47]. Solid-state NMR studies of HETs filaments show remarkably higher resolution than has been previously found for other amyloids, suggesting greater uniformity in structure[48]. The prion domain (residues 218–289) includes four β-strand segments, with homology between pairs of segments[48].

PRION PROPAGATION AND CHAPERONES

Starting with the disaggregating chaperone Hsp104[49,50], many chaperones and their co-factors are crucial to prion propagation, including Hsp70s, Hsp40s, and their co-chaperones [51–58](Fig. 3).

Hsp104 is required for each of the amyloid-based yeast prions[13,50,54], and study of its role in prion propagation is facilitated by a surprisingly specific inhibitor, millimolar guanidine[55,59–61]. In cooperation with Hsp70s and Hsp40s, Hsp104 can disaggregate heat-denatured proteins[62], and is believed to promote prion propagation by breaking up long amyloid filaments to create new seeds[63–66]. Overproduction of Hsp104 cures [*PSI*+], but not [URE3] or [*PIN*+].

Cytoplasmic Hsp70s, (Ssa1 to Ssa4, Ssb1, 2) bind exposed hydrophobic protein segments and help refold the protein in an ATP-regulated process. The Hsp70•ADP form binds tightly, whereas the Hsp70•ATP form rapidly binds and releases the peptide substrate. Mutants of Ssa1 lose [*PSI*+][52] and mutants of Ssa2 lose [URE3][20]. Overproduction of Ssa1 inhibits curing of [*PSI*+] by Hsp104 overproduction[51], but Ssa1 itself cures [URE3][67]. Detailed genetic analysis shows that the Ssa1•ADP form inhibits [*PSI*+] propagation, whereas the Ssa1•ATP form promotes it[58]. Therefore, overproduction of the co-chaperone Sti1p or depletion of the nucleotide exchange factor Fes1p, both of which favor the Ssa•ADP form, impair [*PSI*+] propagation, whereas depletion of Sti1p or overproduction of Fes1p have the opposite effects[58]. It is possible that the tightly binding Ssa•ADP form binds to the growing ends of filaments or to unstructured Sup35p prion domains and prevents filament growth.

As breakage of filaments to form new seeds is believed to be a prime role of Hsp104 in prion propagation[63,65,66], filament breakage by shearing also plays a prominent role in amyloid propagation *in vitro*[68,69]. Direct observations of fibre elongation show that it occurs by monomer addition[69], and the less than expected dependence on monomer concentration of the time lag in amyloid formation is explained best by fibre fragmentation[69], not by addition of oligomers[70].

PRION VARIANTS AND THE SPECIES BARRIER

Mammalian prion 'strains' were identified by differences in incubation period, disease symptoms and signs and distribution of brain lesions despite having the identical PrP sequence[71]. Likewise, variants of yeast prions have been identified based on differing stability and intensity of phenotype[11,12,72,73]. Different variants of [*PSI*+] are based on different amyloid structures[26,27,74], but the precise differences in structure are not yet known. Different prion variants can also have distinct chaperone requirements for propagation[53].

In mammals, the 'species barrier' is the elongated incubation period or inefficient transmission of TSEs from one species to another[75], due to differences in the sequence of PrP[36]. Bovine spongiform encephalitis (BSE) is a distinct variant of TSE that has a reduced species barrier compared with sheep scrapie strains (reviewed by[76]). Collinge has proposed that the PrP of each species is capable of a different range of prion conformations, and that a given prion variant (conformation) can infect those species whose PrP can assume that conformation[76]. Therefore, species barrier is a variant-specific phenomenon (Fig. 4). A similar species barrier with variant-dependence has been shown between, for example, [*PSI*+] based on *S. cerevisiae*, and *Pichia methanolica*[77–81].

PRION GENERATION

High frequency induction of [*PSI*+] by overproduction of Sup35p reqiures [*PIN*+][13] or [URE3] [73] or excess of one of many Q/N-rich proteins, even without forming prions[14,82]. This suggests cross-seeding as the likely mechanism[83]. Each yeast amyloid-based prion can also partially interfere with the propagation of others in some cases[67,84].

Depletion of Ssb1 and Ssb2, two similar Hsp70s associated with ribosomes or of Ubc4, one of the major ubiquitin-conjugating enzymes, can also increase the frequency with which [*PSI* +] arises *de novo*[85,86]. As Ssb1 and Ssb2 are believed to promote proper folding of proteins as they are synthesized, their absence might result in misfolded forms of Sup35p that are more prone to become prions. The Ubc4 defect would be assumed to result in failure to destroy misfolded Sup35p molecules but ubiquitin-conjugated Sup35p was not detectable[85,86].

[*PSI*$^+$] prion generation is also affected by components of the actin cytoskeleton[87]. Interactions of Sla1p, Sla2p, End3p, Arp2p and Arp3p with Sup35NM are detected by two hybrid methods, while *sla1* or *end3* mutants show decreased generation of [*PSI*$^+$] on overproduction of Sup35p[87]. The same mutants show decreased Sup35p aggregates, which may account for the effect on prion generation. The authors suggest that this cytoskeleton - assembly apparatus may be acting like the mammalian aggresome, a perinuclear structure where aggregates are accumulated.

ARE FUNGAL PRIONS A HELP OR A HINDRANCE?

Although most amyloids are associated with pathogenic processes, several are known to be functional for the host. The 'curli' amyloids on the surface of certain bacteria promote adhesion that is important in colonization[88]. Amyloids provide a stable outer coat to certain fish eggs[89] and amyloid 'hydrophobins' coat fungal cells[90]. Amyloid may also play a role in melanin biosynthesis[91]. Are any yeast or fungal prions similarly advantageous?

The [Het-s] prion carries out heterokaryon incompatibility, a process used by most (or all) filamentous fungi apparently to prevent infection with debilitating fungal viruses. Therefore, the demonstration that [Het-s] was a prion[19] suggested that this was the first prion to have a role for the cell[92]. The [β] prion is necessary for meiosis and for survival in stationary phase[20], indicating that this prion is quite beneficial. Based on subtle differences in growth rates under various laboratory conditions, it was suggested that [*PSI*$^+$] helps yeast to evolve[93]. However, this approach would require determining to what extent these growth conditions are represented in the yeast ecological niche, and whether in such conditions [*PSI*$^+$] yeast is more likely to be found[94]. Moreover, survival under non-growth conditions may be as important as rates of growth.

An alternate approach was to survey for yeast prions in wild strains[95]. Infectious agents can be widespread in nature in spite of often being a severe detriment to their hosts. Prions are no exception to this rule, as scrapie of sheep and chronic wasting disease of deer and elk can be frequent enough to seriously impact herds in captivity or in the wild. Certainly, an infectious entity which is also an advantage to its host would become widespread in natural populations, particularly one which, like the yeast prions [URE3] and [*PSI*$^+$], arises *de novo* at rates as high as 10^{-6}, precluding absence because of failure of exposure of the population. Therefore, it was reasoned, a prion that is not found in wild yeast must be detrimental to its host[95]. As controls, the mildly detrimental nucleic acid replicons 20S RNA, 23S RNA, L-A dsRNA virus, L-BC dsRNA virus, and 2 μm DNA plasmid were readily found in wild isolates. However, neither [URE3] nor [*PSI*$^+$] was identified in any of 70 wild isolates. A few wild strains examined by others also failed to turn up [*PSI*$^+$][78,96]. This indicates that these prions cause diseases in yeast[95]. However, [*PIN*$^+$] is occasionally found in wild strains, similar in frequency to the

mildly growth-slowing nucleic acid replicons[95,96]. Since [*PIN*$^+$] arises *de novo* at rates many orders of magnitude higher than do the DNA and RNA parasites, but is limited in its occurence, it is probably mildly detrimental.

In contrast to the yeast [*PSI*$^+$] and [URE3] prions which are at least rare in wild strains (if not absent entirely), [Het-s] is found in 80% of wild isolates with the *het-s* allele[97]. This is consistent with the idea that [Het-s] is benefiting its host, but another possibility has emerged from genetic analysis of [Het-s]. In crosses of female *het-s* [Hets] cells with male *het-S* strains, there is selective lethality of *het-S* segregants in a reaction like the incompatibility reaction of vegetative cells[97]. This apparently constitutes a meiotic drive system in which *het-s* promotes its inheritance not by benefiting the organism but by killing off individuals that inherit the alternate allele.

Another argument advanced for a functional role of yeast prions is that 'prion domains', N-terminal regions of Sup35p and Ure2p homologues not essential for function of the protein, have been maintained in evolution, and some have been shown to be capable of prion conversion in *S. cerevisiae*[77,78,98], and so prion formation must be important for the cell. However, Aigle's group[99] showed that although the *Saccharomyces paradoxus* Ure2p has an N-terminal Q/N-rich region only slightly differing from that of *S. cerevisiae*, it does not undergo a prion change at detectable frequency in *S. paradoxus*. In addition, the C-terminal domain complementation of *ure2*Δ is incomplete without overexpression, showing that the prion domain functions in nitrogen regulation, like the rest of the molecule[100]. Moreover, studies in *S. cerevisiae* and *P. anserina* indicate functions for the prion domain of Sup35p independent of prion formation[101,102]. Therefore, these N-terminal extensions do not necessarily enable prion formation and are involved in the function of the protein without forming prions. Prion formation may be viewed as a rare unfavorable consequence of these important domains, much as the occurrence of Creutzfeldt-Jakob disease, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis do not explain the conservation in evolution of PrP, Aβ precursor protein, α-synuclein and superoxide dismutase. In summary, the [URE3], [PSI+] and probably [PIN+] prions are a hindrance, the evidence for [Het-s] favors it being a help, and [β] is clearly helpful.

Future prospects

What is the scope of the prion phenomenon? The presence of four prions in *S. cerevisiae* and two in *Podospora anserina* argues that there are more to be found. There are many self-modifying enzymes; might some of these, as in the case of [β] and [C], under some circumstances become prions? Are there more useful amyloids like [Het-s] or more debilitating ones? Yeast prions are already being used to screen for anti-prion drugs that are active against mammalian prions[103]. What is the structural basis of the amyloids that are central to the prion phenomena? The parallel in-register β sheet structure of [*PSI*+] still leaves open the issues of the details of this structure, the structural basis of prion variants, whether other amyloid prions will have similar structures, and the difference(s) between infectious and non-infectious amyloids. How does the bewildering array of chaperone effects on prions translate into mechanisms of promoting propagation or curing? This area will likely clarify the nature of prions, chaperones and the wider problem of amyloid diseases.

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Glossary

Prion, Infectious protein (with no needed nucleic acid for infectivity).; Prion seeds, Amyloid fragments that can grow, be again fragmented and thus propagate the prion. Similarly, active enzyme molecules of the [β] and [C] prions act as seeds.; Non-Mendelian (or non-chromosomal or cytoplasmic) genetic element, A gene or replicon that in inherited or transmitted independent of the chromosomes, such as the mitochondrial genome, the 2 micron plasmid, a yeast virus or, as discussed here, a prion.; Amyloid, A filamentous form of protein with a cross β-sheet structure. That is, the β-strands are perpendicular to the long axis of the filaments; Parallel β-sheet, Adjacent β-strands are oriented in the same N- to C- terminal direction.; In-register parallel β-sheet, Each residue is aligned with the same residue of the adjacent strand:; Nuclear magnetic resonance, (NMR). Using solid-state NMR distances between labeled nuclei can be measured by the rate of decay of signal due to dipole-dipole coupling.; Gene gun, A device using a pneumatic gun to propel gold particles coated with DNA or protein into cells to genetically transform them..

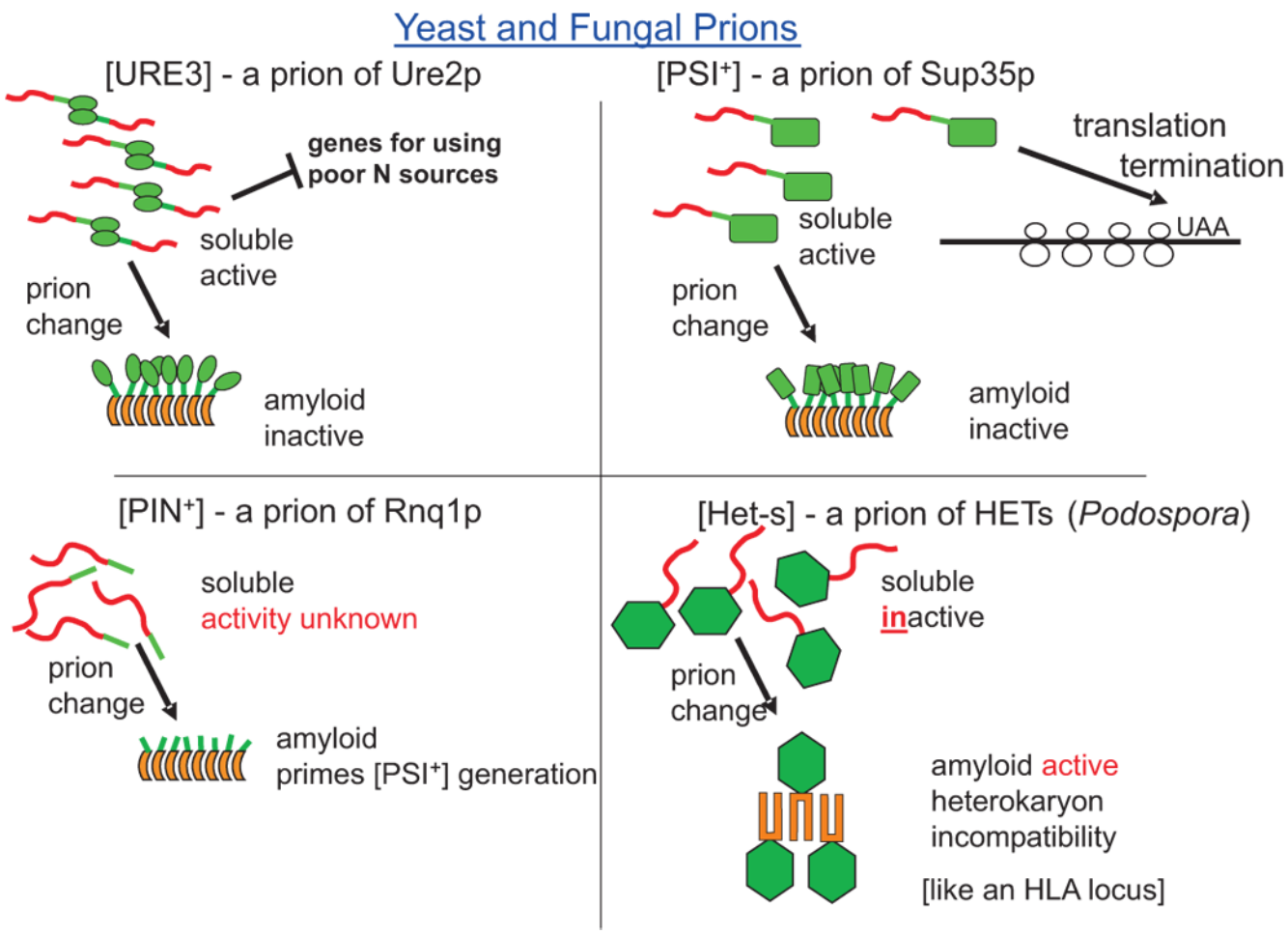

Figure 1. Yeast and fungal amyloid prions

The soluble forms of Ure2p and Sup35p function in nitrogen regulation and transcription termination, respectively. Their amyloid forms are non-functional. Soluble Rnq1p has no known cellular function and the amyloid form can sporadically prime polymerization of Sup35p or Ure2p resulting in generation of the [*PSI*$^{+}$] and [URE3] prions. The soluble form of the HETs protein has no known function, but its amyloid form is necessary for heterokaryon incompatibility, a limitation on fusion of neighboring colonies. Red domains are apparently unstructured in the native form and become amyloid in the prion form. Green shapes are natively structured domains.

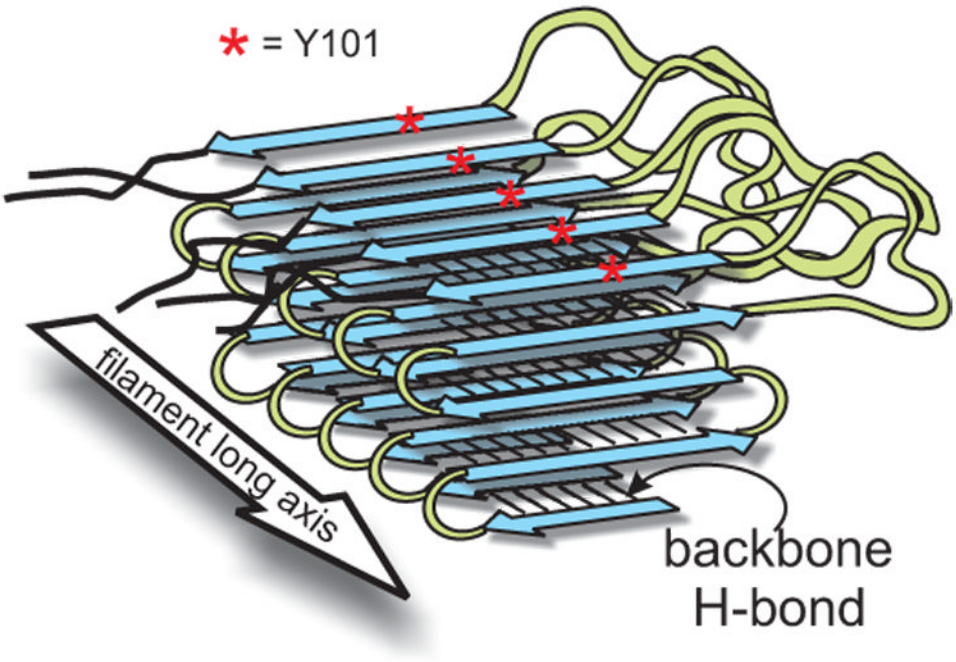

Figure 2. Sup35NM structure model

Parallel in-register β-sheet structure of the prion domain of Sup35p[43]. β-strands (blue arrows) run perpendicular to the long axis of the filaments and are connected by loops (green). A given residue (such as Tyr101) is aligned with the same residue in the adjacent strand (red). This structure can explain the transmission of prion variant information, as the entirety of each prion domain contacts those of the next and previous molecules in the filament.

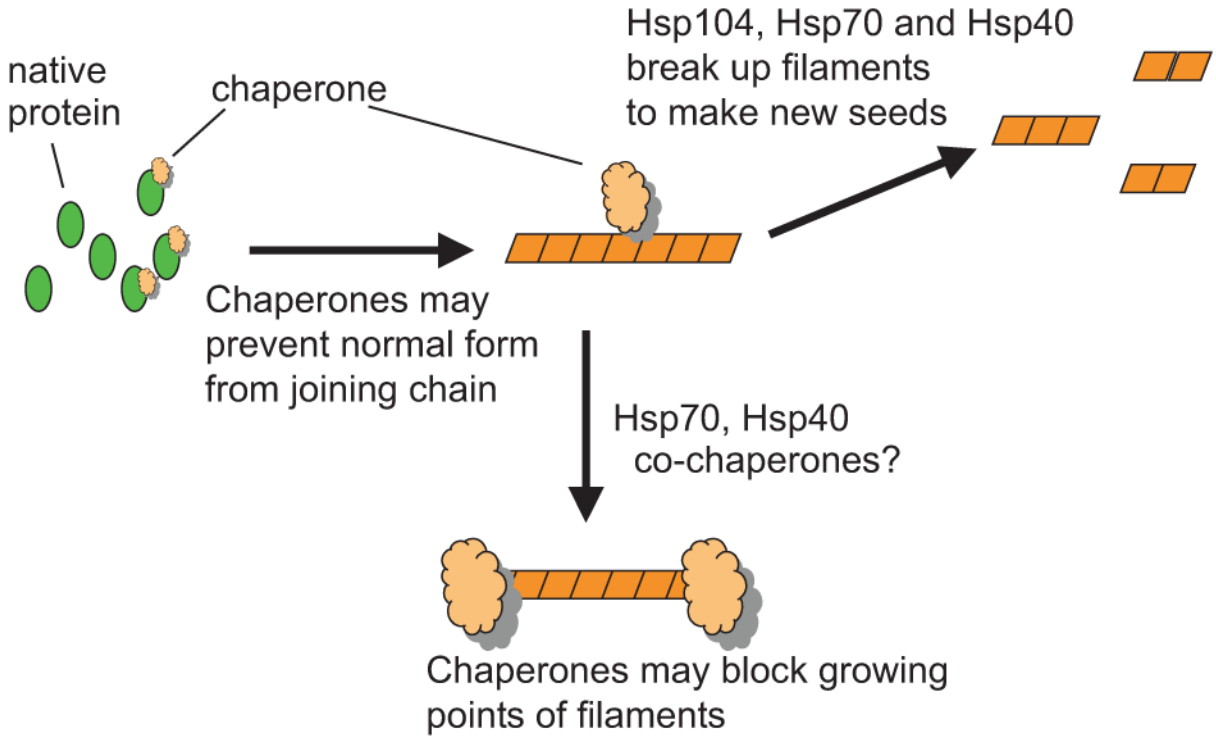

Figure 3. Chaperones and prions

Chaperones (tan shapes) may help prion propagation by breaking long amyloid filaments into shorter ones thereby creating new growth points for amyloid formation (seeds). Chaperones may also hinder prion propagation by binding to the ends of filaments thereby blocking their growth or by binding to the soluble form of the protein thereby preventing the protein from joining the chain. Certainly Hsp104, and probably the cytoplasmic Ssa Hsp70s, have a role in filament breakage.

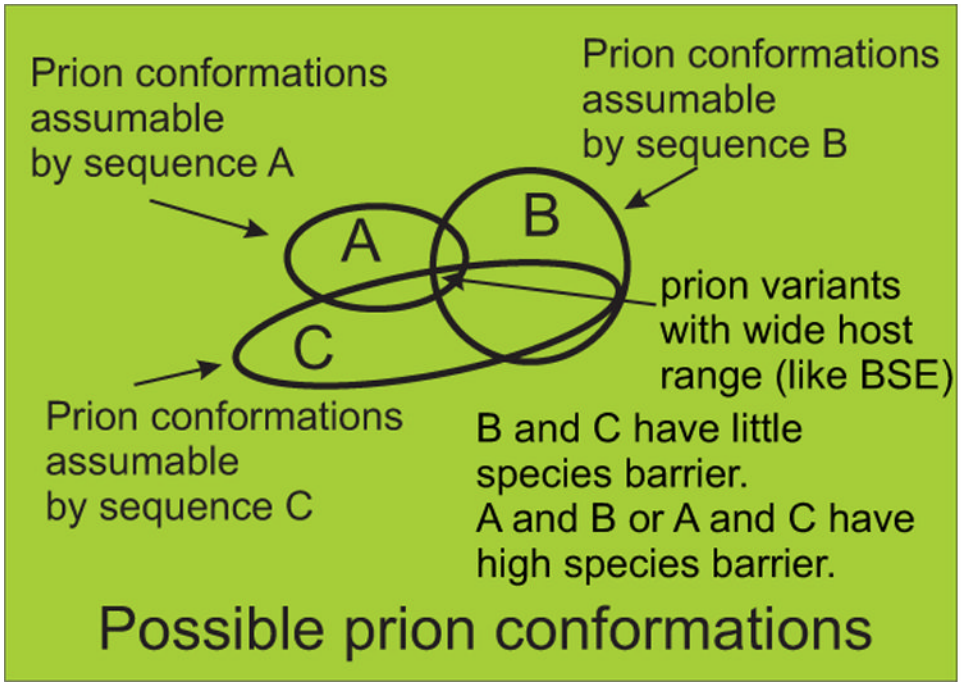

Figure 4. Prion variants & species barrier

Sheep scrapie shows limited infectivity for goats, a phenomenon called the species barrier. The overlap of conformations that donor and recipient proteins can assume determine the strength of the species barrier[76]. As species B and C have prion proteins able to assume many similar amyloid conformations, there will be little species barrier between them. Prion protein of species A and C have few common conformations and so will have a high species barrier. A prion variant (such as bovine spongiform encephalopathy) due to an amyloid conformation that can be assumed by the protein sequence of many species will have a broad host range.

Table 1

Prions and Their Effects

Prion	protein affected	phenotype	mechanism of phenotype
TSEs	PrP	neuronal vacuolation, astrocytosis, neuronal loss, ataxia, dementia, death	possibly internalized oligomeric PrP interference with intracellular endosomes and secretory system
[URE3]	Ure2p	derepression of genes for utilizing poor nitrogen sources, slowed growth	failure to retain Gln3p in cytoplasm
[*PSI*$^+$]	Sup35p	read-thru of translation termination codons	inactive translation termination factor
[*PIN*$^+$]	Rnq1p	ability to induce [*PSI*$^+$] appearance by Sup35p overproduction	cross-seeding by Rnq1p amyloid of Sup35p amyloid
[Het-s]	HETs	heterokaryon incompatibility	?
[β]	vacuolar protease B	death in stationary phase, failure in meiosis	failure to degrade cellular proteins under N starvation
[C]	MAP kinases	slow growth, increased pigment	?