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Are prions part of the dark matter of the cell?

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The [*PSI*$^+$] determinant in *Saccharomyces cerevisiae* is the prion protein corresponding to the eRF3 translation termination factor. Numerous infectious proteins have been described in yeast, in comparison of the unique PrP protein in higher eukaryotes. The presence of the PrP prion is associated with mammalian diseases. Whether fungal prions are beneficial or deleterious are still under discussions. The review focuses on [*PSI*$^+$]-induced phenotypes and the resulting physiological consequences to shed light on the cellular changes occurring in a [*PSI*$^+$] cell and its possible role in nature. To date, only two genes directly regulated at the translational level by [*PSI*$^+$] have been identified. Yet, through all the published works, obtaining a consensus for the described [*PSI*$^+$] phenotypes appeared a tricky task. They are highly dependent on the prion variant and the genetic background of the strain. The [*PSI*$^+$] prion might generate diverse modifications not only at the translational, but also at the transcriptional levels, and the phenotypic heterogeneity is the result of these complex combinations of the genotypic expression.

The term "prion" was first used by Prusiner[1] to refer to an infectious protein that does not need an accompanying nucleic acid. This term was used to describe the pathogenic agent of the bovine spongiform encephalopathy, which can be transmitted to humans causing a new variant of the Creutzfeldt-Jacob disease (CJD). These diseases are linked to a conformational conversion of the cellular prion protein PrP^C into a pathogenic form called PrP^{Sc}, which is strongly resistant to denaturing reagents. This pathogenic form is believed to propagate by binding to PrP^C and acting as a template to modify the folding of neo-synthesized PrP proteins.

The term "prion" was initially used to distinguish the protein-based infectious agent from conventional pathogens. The concept has since been extended to fungi (yeast and filamentous fungus, *Podospora anserina*) and could probably be extended to many more organisms. Three properties are common to all known fungal prions: (1) Prions display a non-Mendelian segregation and are transmitted through the cytoplasm; (2) The gene encoding the prion protein is necessary for propagation of the prion; (3) once a prion is eliminated from a cell, it may reappear spontaneously (due to the presence of the endogenous protein in its soluble form); (4) Prions are self-perpetuating protein conformations.

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Yeast prions were first identified as non-Mendelian traits inherited through the cytoplasm.[2] These prions, called [*URE3*] and [*PSI*$^+$], arise from self-replicating conformations of proteins encoded by chromosomal genes *URE2* and *SUP35,* respectively.[3-6] Definitive evidence has been provided by the demonstration that [*PSI*$^+$] can be induced by infecting yeast with pure prion protein and that different conformations of stable Sup35 amyloids induce different [*PSI*$^+$] variants.[7] This proof of principle has also been demonstrated with the yeast [*URE3*] and [*PIN*$^+$] prions and *P. anserina* [Het-s] prion.[8-11] Since the discovery of the two initial prions, several new prion proteins have been identified in yeast: Rnq1p/[*PIN*$^+$],[12,13] Swi1p,[14] [*GAR*$^+$],[15] Cyc8p,[16] Mot3p,[17] Sfp1p[18] and also New1p[19] carrying a prion like domain. More recently, a bioinformatics scan of the yeast genome revealed at least 19 new candidates have a domain that can display prion properties and are therefore strong candidates for additional prions in yeast.[17] These studies indicate that prion proteins are more frequent than previously anticipated. This raises interesting questions about the physiological relevance of all these prions, as well as the expected number of prions in other organisms such as humans.[20]

Prion formation and maintenance are highly dependent on cellular factors in particular molecular chaperones.[21,22] Hsp104p plays a major role in both the generation and propagation of [*PSI*$^+$].[23,24] Hsp104p is involved in protein disaggregation and is required for protein nucleation, the preliminary step before [*PSI*$^+$] or [*URE3*] prion formation.[25,26] Indeed, one can propose that in vivo the main function of HSP104 is to fragment the large prion aggregate. Evidence is now emerging that even if prions may require similar cellular machinery for their propagation, their sensitivity to molecular chaperones may differ, possibly due to tiny structural differences.[27,28]

[*PSI*$^+$] has been one of the most studied prions. Many studies focused on the physiological role of this prion. [*PSI*$^+$] is the prion form of the eukaryotic release factor 3 (eRF3) a translation termination factor, which, together with eRF1, promotes translational arrest, peptide release and probably ribosome dissociation.[29,30] The conformational change impairs the termination activity of eRF3, thus increasing stop codon readthrough, and affects mRNA stability [through the "Non-sense mediated decay" (NMD)]. The ability of Sup35p to switch into a prion conformation and the regulation of this switch by the protein remodeling factor Hsp104p have been conserved over a million

years of fungal evolution.[31,32] Many phenotypes are associated with the appearance of [*PSI*$^+$] and are linked with a defect in termination.[33,34] However, whether [*PSI*$^+$] causes a selective disadvantage or induces phenotype diversity remains unclear.[35-37] The absence of [*PSI*$^+$] in wild yeasts is suggestive of a detrimental role for [*PSI*$^+$],[38] consistent with a potential defect in translation termination. However, this detrimental function could be counterbalanced by the transient presence of [*PSI*$^+$] during stressful periods, facilitating the rapid adaptation of cells in a fluctuating environment. This would be consistent with the conservation of the eRF3 prion domain and of its capacity to switch into a prion conformation over the past one hundred million years.[39,40] This domain is not required for the termination activity of eRF3; its conservation in distantly related to budding yeast species, such as *Candida albicans*, *Pichia methalonica* and *Saccharomyces cerevisiae,*[39,41-43] thus suggesting that it fulfils another physiological role.[44] The [*PSI*$^+$] prion may act as a possible evolutionary capacitor based on its positive effect on evolvability[45] and the fact that its induction/loss frequencies respond to environmental stresses.[35,46] Nucleotides upstream and downstream from the stop codon have a profound impact on termination efficiency.[47,48] Thus, in the presence of [*PSI*$^+$], not all termination codons will be subject to readthrough. Indeed, the number of genes affected by the presence of [*PSI*$^+$] and the phenotypic consequences are unknown. Numerous attempts to identify an adaptive function of the Sup35p prion state were made by systematic comparison of various phenotypes between several isogenic pairs of [*PSI*$^+$] and [*psi*$^-$] strains. True and Lindquist have submitted seven isogenic pairs of strains to more than 150 phenotypic tests.[36] The growth rate was compared for different carbon or nitrogen sources, and after addition of salts, metals or various inhibitors. Growth at diverse temperatures as well as stress assays (ethanol and thermotolerance) were also analyzed. Indeed, they established that for half growth conditions, at least one [*PSI*$^+$] strain behaves differently from the isogenic [*psi*$^-$] strain. The spectrum of [*PSI*$^+$] strain behavior occurs to be wide. It ranges from complete growth inhibition to substantial growth advantage depending on growth conditions and strain genetic background. Interestingly, the presence of [*PSI*$^+$] is beneficial in more than 25% of the conditions tested whereas translation termination deficiency should be deleterious. Another beneficial [*PSI*$^+$] advantage might be the expression of essential genes carrying a nonsense mutation, as reported by Lindquist and Kim.[49] They described a nonsense mutation within the essential *HSF1* gene encoding a transcription factor that controls the constitutive expression of heat shock proteins and their heat-induction. The nonsense mutation suppression mediated by [*PSI*$^+$] and leading to the production of the full-length essential protein renders the strain viable. Eaglestone et al. also reported enhanced thermotolerance and chemotolerance for [*PSI*$^+$] strains compared with [*psi*$^-$] strains.[35] Those studies clearly established that [*PSI*$^+$] strains behave differently and that the accompanying phenotypes are in some cases beneficial. Sup35p being a factor involved in translation termination, one might expect that perturbing the translation fidelity in [*PSI*$^+$] strains by using antibiotics results in similar phenotypes. Interestingly, no common behavior was observed among the tested strains.[36] Likewise, the presence of Sup35p aggregates might enhance heat shock protein synthesis and consequently stress tolerance. Once again, no identical responses to stress exposure were reported. In conclusion, the presence of [*PSI*$^+$] does not drive identical phenotypes in different strains. Moreover, presence of [*PSI*$^+$] can sometimes have opposite consequences on growth of different genetic background cells. This lack of consensus led the authors to propose that genetic background supersede [*PSI*$^+$] effect. The molecular basis of this phenotypic diversity can be attributed to stop codon readthrough either individually or in combination with the presence of proteins aggregates or loss/acquisition of other prion proteins (see below). To distinguish between these three causes, mutant strains were constructed and submitted to phenotypic tests. In particular, the impact on translation termination was analyzed by the use of mutations within the C-terminal part of Sup35p altering the termination function.[33,35] It appeared clearly that the majority of the phenotypes linked to the presence of [*PSI*$^+$] were due to decoding of translation termination signals. However, analysis of the progeny arising from crosses between [*PSI*$^+$] strains exhibiting a different phenotypic spectrum failed to identify particular molecular targets, as the traits were probably controlled through multiple genetic changes. Nevertheless, it revealed that some traits became independent from [*PSI*$^+$], raising the important question of the fixation of cryptic genetic variations. This study points to the fact that fidelity of translation termination is central to [*PSI*$^+$] physiology. Noteworthy, the strain-associated [*PSI*$^+$] variant was never analyzed during these studies and the observed phenotype variability might indeed be related to the presence of prions of different strength.

Some candidate genes, which might contribute to the phenotypic diversity, have been identified (**Fig. 1**). The *PDE2* gene, encoding the high-affinity cyclic AMP phosphodiesterase, is subjected to stop codon translational readthrough under the control of [*PSI*$^+$].[50] The generated protein harboring a carboxy terminal extension is significantly altered in stability, resulting in increased intracellular cAMP concentration. The cAMP signaling is known to modulate a variety of cellular functions, such as carbohydrate metabolism, cell growth, differentiation, gene transcription and stress responses.[51] Phosphodiesterases play a key regulatory role, as degradation is the only way to inactivate cAMP. Although *PDE2* is not an essential gene in yeast, genetic interactions were revealed with many other genes, which significantly influence stress response, nutrient utilization and the life span of the cell.[52] Control of *PDE2* activity is a critical step for determining intrinsic stress resistance of yeast cells.[53] Its deletion rendered cells sensitive to freeze-thawing, peroxides, paraquat, cycloheximide, heavy metals, NaCl, heat or cold shock. The decreased translation termination of the *PDE2* gene, leading to destabilization of the protein, may account in an unknown extent for a large proportion of the [*PSI*$^+$]-dependent phenotypes. Whether this effect is direct or indirect remains to be determined.

The other candidate gene identified as being under the control of [*PSI*$^+$] is *OAZ1.* This gene encodes the ornithine decarboxylase antizyme, described for its regulation of ornithine decarboxylase (ODC) (**Fig. 1**). ODC is a rate-limiting enzyme in the biosynthesis of polyamines. Polyamines such as spermidine

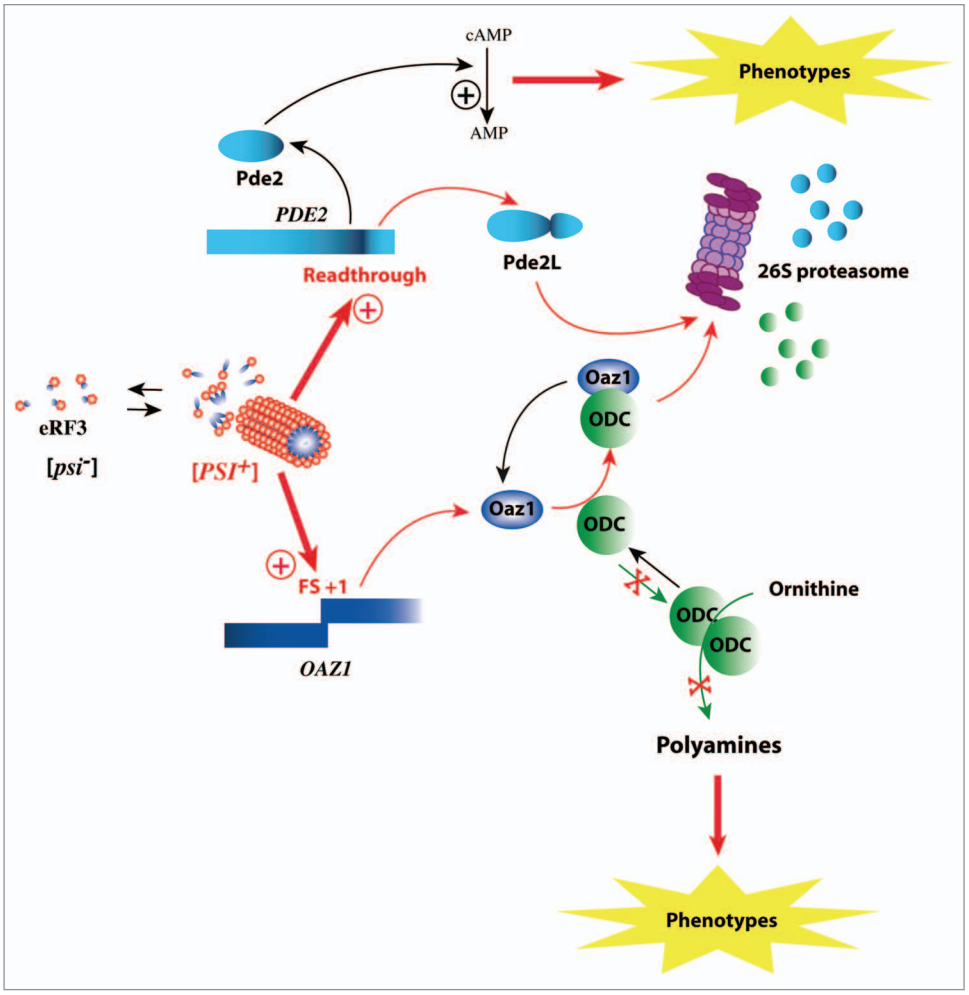

Figure 1. The expression of two genes directly influenced by the prion [*PSI*⁺]. The appearance of [*PSI*⁺] increases stop codon readthrough efficiency of the PDE2 gene. The longer protein (Pde2L) is rapidly degraded by the proteasome reducing the total amount of Pde2 proteins in the cytoplasm. This leads to a global reduction of cAMP level within the cell resulting in the appearance of several phenotypes. [*PSI*⁺] also induces stop codon dependent frameshifting increasing the expression of the antizyme. The increased amount of functional antizyme reduces the overall polyamine concentration. At least half of the [*PSI*⁺]-dependent phenotypes are due to a modification of polyamine content.

and spermine are essential aliphatic organic polycations present in prokaryotes and eukaryotes. They have been implicated in many processes ranging from translation, replication and prion formation to aging.[54] The antizyme binds to ODC and promotes its ubiquitin-independent degradation via the 26S proteasome.[55] The antizyme levels increase with rising intracellular polyamine concentrations. This process involves the induction of a programmed ribosomal frameshift during decoding of the *OAZ1* gene. This programmed frameshifting depends on the presence of a shifty-stop located in the ribosomal A-site during frameshifting.[56] We recently provided important insight on this issue by demonstrating that a [*PSI*⁺]-induced defect in translation termination stimulates expression of the *OAZ1* gene.[34] The presence of [*PSI*⁺] increases the ribosomal pause at the antizyme shifty-stop, stimulating the production of the protein, which leads to a greater degradation of ODC, and then to a decrease in polyamine levels. In yeast, modification of the cellular content of polyamines by the prion accounts for half of the 22-tested [*PSI*⁺]-induced phenotypes. This study opens new possibilities for the role of [*PSI*⁺], which influences cell physiology not only by nonsense codon suppression, but also by modulation of the translational reading frame.

Besides these directly [*PSI*⁺]-controlled genes, the change of prion content is also correlated with modifications of the mRNA turnover or the aggregation state of various proteins. Indeed, some [*PSI*⁺] phenotypes can be resumed by inactivation of the NMD RNA helicase Upf1p.[33,57] The NMD surveillance complex recognizes premature translation termination events and provokes rapid degradation of the mRNA.[58] Thus, stabilization of NMD mRNA substrates partially explained the [*PSI*⁺] phenotypes. Other investigations suggest a possible impact of prion aggregates-associated proteins.[59,60] Nevzglyadova et al. identified a large group of such proteins (chaperones, glucose metabolism enzymes, proteins involved in translation and oxidative stress response), whose aggregation may act on the cell physiology and participates to the [*PSI*⁺] phenotypes.

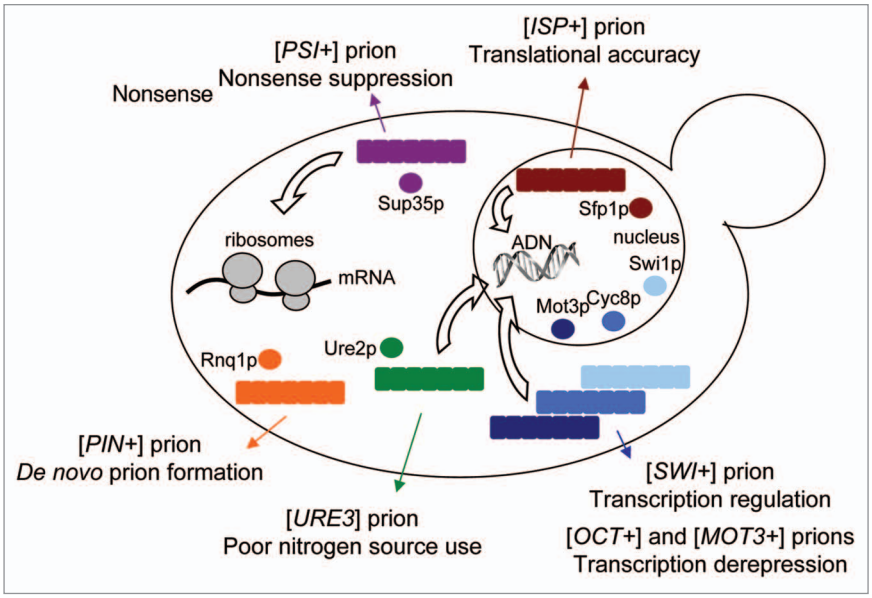

Figure 2. Amyloid-based prions in *Saccharomyces cerevisiae*. Schematic representation of the soluble and aggregated proteins in the yeast cell. The prion-associated phenotypes and the targeted processes are indicated by colored and white arrows, respectively.

In a same way, the prion state of a protein may influence probability of prionization of another protein,[12,61-63] which opens a possibility for concerted modification of several proteins at once. Thus the presence of [*PSI*$^+$] may induce the appearance of other prions, and the observed phenotypes due to a combination of all. Yet, both mechanisms need do be further established. To date multiple amyloid-based prions have been described in the yeast *Saccharomyces cerevisiae* (**Fig. 2**), as well as two self-perpetuating determinants of non-amyloid nature, [β] and [*GAR*$^+$].[15,64]

Du and colleagues[14] identified the [*SWI*$^+$] prion linked to the chromatin-remodeling factor Swi1. The SWI/SNF complex is evolutionarily conserved and has a regulatory role in gene expression, being responsible for the transcriptional regulation of approximately 6% of the yeast genome.[65] Formation of the [*SWI*$^+$] prion results in a partial loss-of-function phenotype for Swi1, including poor sporulation and a reduced ability to grow on raffinose as a sole carbon source. Another global transcriptional regulator, the Cyc8 protein is also able to form a prion [*OCT*$^+$].[16] The evolutionarily conserved Cyc8p-Tup1p transcriptional repressor complex controls the expression of over 7% of yeast genes involved in a wide variety of physiological processes.[66] Therefore, interplay of both complexes determines the expression fate of many genes by remodeling chromatin in promoter and upstream regions. Thus prionization of Cyc8 and Swi1 might have a functional role in creating novel phenotypes.

In a recent genome-wide screen for yeast prion candidates, another globally acting transcription factor, the Mot3p protein, was reported as propagating the [*MOT3*$^+$] prion.[17] The [*MOT3*$^+$] cells exhibit a loss-of-function phenotype for Mot3p, which modulates a variety of processes, including mating, carbon metabolism and stress response.[67] Moreover further investigations are needed to better specify the phenotypic variations induced after the protein conformational change.

Recently, the [*ISP*$^+$] prion form of, once again, a global transcriptional regulator, the Sfp1 protein, was demonstrated.[18] Expression of ~10% of all yeast genes is positively controlled by Sfp1, including genes that encode ribosomal proteins and other components of the translational machinery.[68] The Sfp1 prionization causes antisuppression, larger cell size and increased resistance to drugs targeting translation. Interestingly, in contrast to the other known prions, the [*ISP*$^+$] phenotypes do not correspond to the loss of Sfp1 function. An influence of [*ISP*$^+$] on the status of some other proteins might be inferred by their prionization or sequestration in aggregates. Another unique feature of this prion is its nuclear location (**Fig. 2**). These atypical properties of [*ISP*$^+$] put forward new insights for prion behavior and function within the cell.

Thus numerous prion proteins are positioned at crucial regulatory nodes and could modulate the correlation between genotype and phenotype, as these four known yeast prions corresponding to global transcriptional regulators.

The specific outline of the [*PSI*$^+$] phenotypes remains still obscure. Several investigations highlight some modifiers of [*PSI*$^+$] phenotypes, as the Paf1 complex which is involved in mRNA 3' end processing and polyA site selection.[69] The authors suggest that the Paf1 complex modulates both stability and translatability of some mRNA subjected to [*PSI*$^+$]-mediated readthrough. The nonstop mRNA decay (NSD), a process degrading mRNA with no stop codon, was also described as genetically interacting with [*PSI*$^+$].[57] Strains defective in NSD show a greater variation in phenotypes between [*psi*$^-$] and [*PSI*$^+$] states than corresponding wild-type pairs. These modifiers probably act through mRNA stability and/or translatability and decrease the level of functional C-terminally extended proteins contributing to the phenotype of [*PSI*$^+$] strains. Some phenotypes might thus be hidden and under-estimated.

One way to identify the protein changes induced by the presence of [*PSI*$^+$] would be by proteomic approaches. In collaboration with Jean Labarre (CEA Saclay), we subjected total protein extracts of isogenic [*psi*$^-$] and [*PSI*$^+$] strains to two-dimensional gel electrophoreses. Unfortunately no significant difference was observed between the two patterns (personnal communication).

In conclusion, the [*PSI*$^+$] phenotypes observed can partially be explained by an effect on the two directly regulated *PDE2* and *OAZ1* target genes. Moreover the phenotypic heterogeneity might result from the presence of potentially different prion variants and various genetic backgrounds. Focusing on phenotypes certainly helped to better understand the physiological consequences of the [*PSI*$^+$] prion, nevertheless some specific mechanisms of the de novo appearance or transmission of prions remain still to be elucidated. For example, is [*PSI*$^+$] prion useful to reveal cryptic genetic variations and associated phenotypes, or just a by-product of evolution? Overall despite the advances made in the yeast prion field, there are still many questions left unanswered which are part of the future of prion research.

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